LIZZY SUNNY

Prostate Cancer

An Epidemiological Study in India

ACADEMIC DISSERTATION
To be presented, with the permission of the Faculty of Medicine of the University of Tampere, for public discussion in the auditorium of Tampere School of Public Health, Medisinarinkatu 3, Tampere, on September 2nd, 2005, at 12 o’clock.

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1. INTRODUCTION

Prostate cancer remains one of the most prevalent and least understood of all human malignancies. Pathologic evidence suggests that neoplastic changes of the prostate epithelium begin early in a man's adult life, but do not become clinically evident or relevant until decades later. Some patients live out their lives with a prostate cancer that remains stable for decades without treatment. In other cases, the cancer grows aggressively, responds poorly to therapy, and causes death within a few years. The natural history of this enigmatic disease is heterogeneous, ranging from a benign and indolent course to one that rapidly progresses, causing significant morbidity and mortality (Scardino 2000, Wei and Uzzo 2002).

Cancer of the prostate is primarily a disease of the elderly men. About three-quarters of cases worldwide occur in men aged 65 years or more (Parkin et al. 2005). Prostate cancer has become a major public health burden worldwide with an estimated number of 679,000 new cases in the year 2002. This represents 11.7% of all new cancer cases in men (19.03% in developed countries and 5.30% in developing countries). It is a less prominent cause of death from cancer, with an estimated number of 221,000 deaths (5.8% of cancer deaths in men, 3.3% of all cancer deaths) in the year 2002 (Ferlay et al. 2004). Prostate cancer is now the fifth most common cancer in the world (in terms of number of new cases), and the second in importance in men. The low fatality means that many men are alive following a diagnosis of prostate cancer, making this the most prevalent form of cancer in men (Parkin et al. 2005).

Prostate cancer is the most common malignancy, after nonmelanoma skin cancer, and the second leading cause of cancer death in men in the United States. Despite advances in early detection and treatment, more than 230,000 new cases and nearly 30,000 deaths from prostate cancer are expected in the United States alone in 2004 (Jemal et al. 2004). Prostate cancer will be diagnosed in almost one fifth of U.S. men during their lifetime, yet only 3% of men will be expected to die of the disease. The estimated reduction in life expectancy of men in US who die of prostate cancer is approximately 9 years (Greenlee et al. 2001). It is estimated that one out of every 59 men in Mumbai, India will contract a prostate cancer during their lifetime and 99% of the chance is after he completes the age of 50 (Sunny et al.
A wide range of estimates of the impact of the disease is notable. The disease is histologically evident in as many as 34% of men in their fifth decade and in up to 70% of men 80 years of age and older (Holund 1980, Sakr et al. 1993).

Prostate cancer has become a major health problem in the western world during the last decades of the 20th century. In the European Union it is the second most common malignancy in men, with 134,865 new cases and 55,704 deaths in 1996 (Ferlay et al. 1999). It is now the most common cancer among Finnish men with 3,533 new cases reported in 2001. It is also second after lung cancer as a cause of cancer mortality in Finnish men (Finnish Cancer Registry 2003).

Since the late 1940s, there is a dramatic increase in the identification of prostate cancer cases. This dramatic increase is in part due to the greater frequency of operations for benign disease of the prostate, with the subsequent incidental finding of asymptomatic prostatic tumors, as well as the escalation in the use of new diagnostic technology including transrectal ultrasound guided needle biopsy, computer tomography, and serum testing for prostate-specific antigen (PSA) (Potosky et al. 1995, Jacobsen et al. 1995, Hankey et al. 1999). However, the steady increase in the mortality rates implies that the escalation in incidence is not solely attributable to incidental discovery and early detection, but to a real change in the risk of developing the disease (Miller et al. 1993).

Even though the incidence trend is increasing worldwide (Michel et al. 1993), there are wide variations in the age standardized incidence rates of prostate cancer in different parts of the world and in India the rates are only one tenth of that seen in the Western World (Ferlay et al. 2001). Europeans and American whites have high prostate cancer mortality rates, perhaps the highest reported mortality in the world for prostatic cancer is among American blacks, the lowest rates are found in Asians (Kurihara et al. 1989).

In spite of the high incidence and mortality rate of this malignancy, the etiology of this disease has remained poorly understood. Epidemiological research has identified several possible risk factors which may be useful for prostate cancer prevention and targeting high-risk individuals for early detection intervention. Strategies for reducing the occurrence of prostate cancers will be critical in limiting the morbidity and mortality of this disease. The long latency period of prostate tumors and improved understanding of prostate carcinogenesis suggest opportunities for effective preventive measures (DePrimo et al. 2001).

Prostate cancer is a disease in which the mortality rate is highly variable among populations (Brawley 2003). It has been apparent for several years that the age-adjusted incidence rate as well as death rates from clinical prostate cancer vary dramatically from
country to country, even if one allows for differences in and availability of screening programs (Waterhouse et al. 1982, Watanabe et al. 1984). The prevalence of histologic prostate cancer is remarkably similar around the world, but the clinical incidence varies widely suggesting that even though the initiation rate of prostate cancer is the same but there appear to be differences in the rate of promotion or progression to clinically evident prostate cancer. This interpretation is supported by the increasing risk with migratory changes which suggests that prostate cancer develops as a result of an interplay of genetic and epigenetic events, both of which may be affected by environmental risk factors, perhaps acting as prostate cancer promoters (Yatani et al. 1988, Pienta et al. 1989, Carter et al. 1990).

It is well established that the prostate is hormonally influenced. Carcinogenesis is a process of malignant transformation evolving over time, involving cellular growth and division. There is evidence suggesting that androgenic influences over a period of time encourages the process of prostate carcinogenesis (EI Sheikh et al. 2003). Studies of prostate biology support the concept that dihydrotestosterone is the principal androgen responsible for both normal and hyperplastic growth of the prostate gland. It may be that androgen causes prostate carcinoma. Suppression of dihydrotestosterone synthesis may inhibit carcinogenic transformation. Some preclinical and clinical observations support this hypothesis (Brawley 2003).

The link between androgens and prostate cancer is of great interest to scientists because it may enable them to develop chemoprevention methods. The term chemoprevention refers to the use of drugs to reduce the risk of a disease. Drugs with anti-androgenic effects may be of value in prostate cancer chemoprevention. One such drug, finasteride, is currently being evaluated (Meister et al. 2002). Finasteride has been shown to inhibit growth of prostate cancer cells in vitro and in animal studies (Homma et al. 1997). In a recent study, it has been shown that finasteride prevents or delays the appearance of prostate cancer, but this possible benefit and a reduced risk of urinary problems must be weighed against sexual side effects and the increased risk of high-grade prostate cancer (Thompson et al. 2003). It should be noted that some studies have failed to show any potential effect of finasteride in preventing prostate cancer. A nested case control study using stored sera showed no association between 5-alpha-reductase activity and risk of prostate cancer (Guess et al. 1997). A placebo controlled randomized trial using finasteride, an inhibitor of 5-alpha-reductase, the enzyme that converts testosterone to dihydrotestosterone, is ongoing (Brawley 2003). The recent demonstration that finasteride significantly reduced the 7-year period prevalence of prostate cancer in the Prostate Cancer
Prevention Trial underscores the promise of chemoprevention to reduce the burden of this illness (Thompson et al. 2003). However, further development of effective prevention strategies will require a better understanding of the biology of prostate carcinogenesis.

The focus of the last decade has been on early detection and treatment of prostate cancer. An ideal alternative to the reduction of morbidity and mortality is through primary prevention of prostate cancer. The features of prostate cancer, including prevalence, long latency, deficient screening, significant mortality and morbidity, provide the need and opportunity for chemoprevention.

Prostate cancer is a curable disease only in its localized stage. The prognosis of localized prostate cancer is often good even without curative therapy (Gittes 1991, Berner et al. 1999). Up to 20–40% of all prostate cancers are diagnosed at a clinically advanced stage (Scardino et al. 1994, Dickman et al. 1999, Maattanen et al. 1999), when curative treatment is no longer possible.

The epidemiological studies for prostate cancer conducted in India are very few and are mostly hospital-based. In order to find out some of the important risk factors for the occurrence of this cancer with a special attention to vasectomy, the Indian Council of Medical Research conducted a multi-centric population-based case control study. The three centers involved in this study were Mumbai, Delhi and Bangalore, and as part of my research to find out some of the important risk factors for the occurrence of this disease, I have utilized the case control data collected by our Bombay Population Based Cancer Registry (PBCR), in this multi-centric study. The Bombay PBCR covers an area of 603 sq.km. and have a resident population of 12 million as per the 2001 census and is located in the Maharashtra state of India.
2. REVIEW OF LITERATURE

2.1 A demographic profile of India

(The following information is abstracted from the Population Reference Bureau’s 2000 World Population Data Sheet, the U.S. Bureau of Census International Data Base, the UN Population Division, the CIA’s 2000 World Fact book, and the World Bank.)

India is the 7th largest country in southern Asia with widely varying socio-cultural, religious and dietary practices. Important differences exist in the ways of living of the urban and rural populations. India is second only to China in population and is expected to surpass China’s population with 1.5 billion people by 2040. India reached a population of 1 billion in the beginning of 2000, almost three times its 1951 population of 361 million. As per the census of India 2001, the population of India on 1st March 2001 is comprising of 531,277,078 males and 495,738,169 females, giving a sex ratio of 933 females per 1000 males (Census of India 2001). The population density of India is one of the highest in the world at 324 persons per square km., ten times the density of the United States.

India is divided into 28 states and 7 union territories. In 1998, Hindus comprised about 80% of the population and Muslims were 14%. The other minority religious groups include Sikhs, Christians, Buddhists, and Jains. Caste, class, and religion have often been sources of tension between different communities.

India is largely rural. The past few decades have seen a gradual shift of people to urban areas. The urban population increased from 19% of the total population in 1965 to 28% in 2000.

India had rising rates of population growth from 1921, reaching a peak of 2.5% in 1981. In 2000, the rate was estimated to be 1.8%. By 2025, India may have more people than the entire developed world, including Japan.

The total fertility rate has declined from 6 in 1947 to 3.3 in 2000. It is expected to decline further to the level of replacement by 2020. A major contributor has been the increase in the average age at marriage. In 1961, the average age at marriage for men was 22 years and 16 for women. By 1993, this had increased to 26.5 and 24.5, respectively.
Since independence, the Indian government has emphasized family planning through contraceptive use. In 2000, estimates indicated that 48% of (married) Indian women were using a method of contraception; 43% used a method of modern contraception. Among couples who used any method of contraception, 67% of all use was female sterilization and 10% was male sterilization.

Improved control of diseases has resulted in lower death rates. The death rate per thousand population has decreased from 26.6 in 1955 to 9 in 2000. In the past ten years, the infant mortality rate (per thousand births) has decreased from 96 in 1989 to 72 in 2000, comparable to the average of 74 for South Central Asia.

The decline in death rates since 1955 is largely due to control of major epidemics, in particular the successful malaria eradication program in the 1970s and the extensive childhood immunization program. Government programs in maternal and child health include vaccinations for DPT, polio, tetanus, and other childhood diseases and health care for women, especially pregnant and nursing mothers.

Life expectancy at birth has increased for both males and females. In 1965, life expectancy for males and females was estimated at 46 and 44 years, respectively. These numbers increased to 60 and 61 in 2000.

India has a youthful population structure. In the United States in 2000, 21% of the population is below 15 years and 13% above 65. In India, 36% of its population is below the age of 15 years, and only 4% above 65 (Figure 1).

In India, decennial censuses have been conducted regularly since 1881. The Government of India views the current population growth as extremely serious, particularly in relation to poverty alleviation. Low female literacy rates are cited as an important cause for low contraceptive usage. In 1981, only 18% of females in rural India were literate. Almost 15 years later, the literacy rate for females more than doubled to 37.7% in 1995. The figures are higher for both sexes in urban areas. For example, the state of Kerala, India’s most urbanized and economically developed state, had literacy rates of 94% for males and 88% for females in 2001.
Age pyramid of India, 2000

Age pyramid of U.S.A. 2000

Figure 1. Age pyramids of India and U.S.A., 2000
Male literacy is significantly higher in both urban and rural areas. As per 2001 census (Census of India 2001), the literacy rate for India as a whole is 65% (76% for males and 55% for females). The government of India has set a long-term target for universal elementary education for all children up to the age of 14 years.

Income inequality in India is high. Thirty-five percent of the population was below the poverty line in 1994. Seventy-five percent of the 350–400 million inhabitants who fall below the poverty line reside in rural areas. At the same time, India has the world’s largest middle class (300 million) that was virtually non-existent in 1947.

### 2.2 Cancer registration in India

In all the developing countries, communicable diseases, respiratory and gastrointestinal infections and malnutrition are the important problems to be tackled by public health authorities. Statistics regarding cancer are usually fragmentary and available only from 5% of the Indian population and thus fail to present an accurate and correct picture of the current problem.

India lacks nationwide cancer registration and systematic death registration. In order to gain insights into the extent of the cancer problem, a cancer survey was undertaken in the Mainpuri district of Uttar Pradesh near Agra for a limited period in 1963. In the same year, a population based cancer registry was established in Mumbai to register all cancer patients in the entire population of the metropolis (Jussawalla and Deshpande, 1996). To study the cancer problem in depth throughout the state of Maharashtra, three satellite registries of the Bombay Registry were established. The first satellite registry was established in Pune city in 1972, (Jussawalla and Jain 1979), the second at Aurangabad in 1978, (Jussawalla et al. 1984) and the third at Nagpur in 1980 (Jussawalla et al. 1987). In 1980, a Population Based Cancer Registry was established for Ahmedabad city in Gujarat by the Gujarat Cancer Research Institute (Patel 1986).

Reliable data on cancer incidence has been available from Mumbai since 1964, from Poona since 1972, from Aurangabad since 1978, from Nagpur since 1980 and Ahmedabad since 1983. These registries cover only few urban centres in India, and hence could not be used to extrapolate a nationwide estimate. Considering the paucity of data on the magnitude of the cancer problem in India, the Indian Council of Medical Research (ICMR) initiated the National Cancer Registry Project (NCRP) in 1982, establishing three Population Based
Cancer Registries (PBCR), one each at Bangalore, Mumbai and Chennai and three Hospital Based Cancer Registries (HBCR) in Chandigarh, Dibrugarh and Trivandrum (NCRP 1985).

In 1986, two more urban population based cancer registries were started, one in New Delhi and another in Bhopal. For the first time, a population based rural cancer registry was started by the Indian Council of Medical Research during the subsequent years (1987) in Barshi, situated in the state of Maharashtra. Another rural cancer registry at Karunagappally was initiated in 1990, in the state of Kerala, by the Regional Cancer Centre at Tiruvananthapuram, with funding from the Department of Atomic Energy, Mumbai. The population based Tiruvananthapuram Cancer Registry was initiated in 1994 by the Regional Cancer Centre, Tiruvananthapuram, in collaboration with the International Agency for Research on Cancer (IARC), Lyon, France. The population based Kolkata Cancer Registry was established in 1997 at Chitarangan Cancer Institute, Kolkata, in collaboration with IARC.

The objectives of the National Cancer Registry Project were as follows:

1. to generate reliable data from PBCRs on the magnitude of the cancer problem,
2. to generate authentic data from the HBCRs on cancer patient care parameters, including diagnosis, extent of disease, treatment and outcome, follow-up and survival for clinical epidemiological studies and other relative frequency data,
3. to conduct other epidemiological investigations and to evaluate cancer control measures,
4. to develop human resources in cancer epidemiology.

In order to estimate the cancer burden in India at the national level, NCRP has started the project, ‘Atlas of cancer in India’ in collaboration with WHO in the year 2002. The main objectives of this project are:

1. to obtain an overview of patterns of cancer in different parts of the country;
2. to calculate estimates of cancer incidence wherever feasible.

The overall aim of this Atlas project is to get to know the similarities and differences in patterns of cancer across the country in a relatively cost-effective way using recent advances in computer and information technology transmission. Knowing patterns of cancer across the country would provide important leads in undertaking aetiological research, in targeting cancer control measures and in examining clinical outcomes.

The cancer registries under the National Cancer Registry Programme (NCRP) have provided since 1982 an idea of the magnitude and pattern of cancer in selected urban centers and a couple of rural areas. However, large areas of the population, particularly the
rural areas remain largely uncovered and therefore the patterns of cancer in several urban centers and rural areas remain largely unknown. As mentioned earlier, India is a vast country with populations having varied cultures, customs and habits. The environment differs and so does dietary practices, and socioeconomic status. Important differences exist in the ways of living of the urban and rural populations. Geographic differences in patterns as well as trends of cancer have already been observed among the different registries. Therefore, the broad purpose of this project is to develop an atlas for the whole India.

2.3 Magnitude of the cancer problem

2.3.1 India

The data on the magnitude of the cancer problem in India are mainly based on the population based cancer registries established in the country. Although the area and population covered by these registries is minimal (about 5%), it gives some idea of the extent of the cancer problem in India. The data utilized for assessing the extent of the cancer problem in India are from Bangalore (Urban), Mumbai (Urban), Chennai (Urban), Bhopal (Urban), New Delhi (Urban) and Barshi (Rural) populations. The area covered, population at risk, number of cancer cases registered along with crude and average annual age-adjusted (world population) incidence rates for all types of cancer for most recent period are presented in table 1.

Table 1. Area covered, Population at risk, Number of cancer cases registered with crude (CR) and age-adjusted (AAR) (world population) incidence rates per 100,000 person years for all types of cancers for population based cancer registries in India, 1990-96.

<table>
<thead>
<tr>
<th>Cancer Registry</th>
<th>Area (sq.km.)</th>
<th>Population at risk</th>
<th>Number of registered-cases</th>
<th>CR</th>
<th>AAR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Bangalore (Urban)</td>
<td>276.4</td>
<td>2338641</td>
<td>2113793</td>
<td>10240</td>
<td>11740</td>
</tr>
<tr>
<td>Barshi (Rural)</td>
<td>3713.4</td>
<td>240725</td>
<td>225812</td>
<td>638</td>
<td>766</td>
</tr>
<tr>
<td>Bhopal (Urban)</td>
<td>284.9</td>
<td>636782</td>
<td>573044</td>
<td>2539</td>
<td>2250</td>
</tr>
<tr>
<td>Chennai (Urban)</td>
<td>170.0</td>
<td>2066275</td>
<td>1930251</td>
<td>11366</td>
<td>12355</td>
</tr>
<tr>
<td>Delhi (Urban)</td>
<td>685.3</td>
<td>5059769</td>
<td>4226684</td>
<td>26218</td>
<td>25861</td>
</tr>
<tr>
<td>Mumbai (Urban)</td>
<td>603.0</td>
<td>5676033</td>
<td>4738442</td>
<td>28953</td>
<td>27091</td>
</tr>
</tbody>
</table>

The average annual age-adjusted (world population) incidence rates of all types of cancer for urban areas range from 97.8 to 121.9 for males and 92.2 to 135.3 for females. In males and females, the highest incidence is registered for the Delhi population (121.9) for males and (135.3) for females respectively. In urban males, the lowest incidence is registered for Bangalore population (97.8), whilst in urban females, the lowest incidence is registered for Bhopal population (92.2). The average age-adjusted incidence rate for Barshi (rural population) was noted as 46.2 for males and 57.7 for females.

It is estimated that there are approximately 2–2.5 million cases of cancer in the country at any given time. Nearly 800,000 cases were diagnosed in the year 2000 and 550,000 deaths due to cancer occurred in the Indian population (Ferlay et al. 2001). An estimated number of 6,605 cases of prostate cancers and a total of 565,682 cases of all types of cancers were predicted for India for the year 2001 (Yeole 1997). The tobacco related cancers account for almost a third of all cancers diagnosed in the Indian population.

### 2.3.2 The global scene

Cancer is an increasingly important health problem on every country’s health agenda. The principal factors contributing to this increase are the increasing proportion of elderly people, the greater ability of medical science to control once fatal communicable diseases, and the rising incidence of certain forms of cancer, notably lung cancer resulting from tobacco use (Parkin et al. 2001).

Data on Cancer Incidence and Mortality from cancer registries are regularly published by the International Agency for Research on Cancer (IARC) in the volumes of Cancer Incidence in Five Continents (Parkin et al. 1992).

Figures 2 and 3 show the highest and lowest age adjusted rates in all continents, viz., Africa, Asia, Central and South America, Europe, North America and Oceania (Parkin et al. 1997).

The highest AAR among either sex is seen in the male Black population of San Fransisco in US. Among females, the Maori population of New Zealand have the highest AAR. In both males and females, the highest rates seen in other continents are substantially higher than the AAR observed in the Indian registries. However, the rates in India are comparable with the AAR of the Indian population of Singapore.
Figure 2: International comparisons of age adjusted cancer incidence rates for all sites per 100,000 population, Males, 1990–96
Estimation of the burden of cancer in terms of incidence, mortality, and prevalence is a first step to appreciate appropriate control measures in a global context. The latest results, based on the most recent available international data, show that there were 10.9 million new cases, 6.7 million deaths, and 24.6 million people living with cancer (within 5 years of diagnosis) in the year 2002 (Ferlay et al. 2004). The most common cancers in terms of number of cases were lung (1.35 million), breast (1.15 million), colorectal (1.02 million), stomach (934,000), and liver (626,000). The profile varies greatly in different populations, and the evidence suggests that this variation is mainly a consequence of different lifestyle and environmental factors, which should be amenable to preventive interventions (Ferlay et al. 2004). World population growth and ageing imply a progressive increase in the cancer burden—15 million new cases and 10 million new deaths are expected in 2020, even if current rates remain unchanged (Parkin et al. 2001).
At least one-third of the new cases of cancer each year are preventable by such means as controlling tobacco and alcohol use, healthy diet, and immunizing against viral hepatitis. Early detection, and therefore prompt treatment, of a further one-third of cases is possible where resources allow. Effective techniques for pain relief are sufficiently well established to permit comprehensive palliative care for the remaining, more advanced, cases. The establishment of a national cancer control programme, tailored to the socioeconomic and cultural context, should allow countries to effectively and efficiently translate the present knowledge into action (Parkin 2001).

2.4 Descriptive epidemiology of prostate cancer

Prostate cancer is one of the few sites of cancer where the difference in incidence rates between that seen in India and western countries is enormous (Figure 4). Even though the rates in India are less than one tenth of the rates seen in the United States and one fifth of the rates seen in UK, it is important to observe the rise in trend in the forthcoming years in India and the future burden (NCRP 2002).

![Figure 4: International Comparison of AAR for Prostate Cancer, 1990–96](image-url)
From many epidemiology studies, it has become clear that there are environmental as well as genetic contributions to the development of prostate cancer. Several series have identified variations in the incidence of prostate cancer based on ethnicity or immigration status. Cook et al. (1999) reported on the incidence of prostate cancer among Asian men born in China, Japan, and the Philippines, compared with US-born Chinese, Japanese, and Philippine men. In this study, the incidence of prostate cancer was approximately twice as high in the US-born men, indicating that lifestyle characteristics may affect the likelihood of developing prostate cancer. Of interest, however, among US residents the annual incidence for all generations of Asian-Americans was roughly half that of white men born in the US. It is unclear whether these differences reflect a genetic component, a lifestyle difference, or both (Cook et al. 1999).

The association of prostate cancer mortality with diet, tobacco use, socioeconomic factors, and health indicators from 59 countries provided by United Nations sources was reported by Hebert et al. (1998). Prostate cancer mortality was inversely associated with the estimated consumption of cereals, nuts, and fish. In the 42 countries for which there were data, soy products were found to be protective. Even in populations with a low risk of prostate cancer, diet appears to affect carcinogenesis. A case-control study found that men in China with prostate cancer were more likely than controls to consume food with a high fat content (Lee et al. 1999). These data suggest that prostate cancer incidence and perhaps mortality are associated with high fat intake, both in high-and low-risk populations.

The epidemiology of prostate cancer gives us some clues that its etiology is likely both environmental and genetic. Countries in which dietary fat intake is greater have been shown to have higher prostate cancer mortality rates leaving some to conclude that dietary fat causes prostate cancer. Migration studies show that men moving from Japan and China adopt increased risks of prostate cancer. Second and third-generation Japanese Americans and Chinese Americans actually have risks of prostate cancer similar to white American men. This is highly suggestive that prostate cancer has an environmental influence. The differences in black-white mortality and newer data suggesting a higher mortality among Jamaican and Brazilian men of African descent suggest there may be a genetic predisposition to prostate cancer. Some have suggested certain polymorphisms increase prostate cancer risk, whereas others are searching for genetic mutations that may increase prostate cancer risk. Africans may have an increased prevalence of these genetic risk factors (Brawley et al. 1998). Ultimately, most investigators agree that prostate cancer results from an interplay between genetic factors, endogenous hormones and environmental

2.5 International trends in prostate cancer incidence and mortality

Prostate cancer has become a major health problem in industrialised world during the last decades of the 20th century. It is now the most common male cancer in the USA (Jemal et al. 2004) and in the European Union it is the second most common malignancy in men (Ferlay et al. 1999).

During the last 20 years, prostate cancer incidence has undergone some of the most dramatic swings observed in cancer statistics. In the USA the incidence of prostate cancer increased by 30% from 80 to 105 per 100,000 men between 1980 and 1988, with a 2.5% rise in the mortality from the disease (Ries et al. 1999). From 1989 to 1992, the incidence of prostate cancer increased, on average, 20% per year, reaching the peak incidence of 179 per 100,000 men in whites in 1992 and 250 per 100,000 in blacks in 1993 (Hankey et al. 1999). Since 1993, a decreasing incidence trend, at a rate of 10.8% per year, has been observed, and in 1997, the average incidence of prostate cancer in the USA was 149.7 per 100,000 men (Hankey et al. 1999, Ries et al. 2000).

Similar trends have been reported in Canada (Mercer et al. 1997), the UK (Chamberlain et al. 1997), France (Grosclaude et al. 1997), Australia (Threlfall et al. 1998), and The Netherlands (Post et al. 1998), although, in general, they are less marked, or occur later, than in the USA.

Until 1992 there was a steady increase in the risk of prostate cancer in all the Nordic countries, while the risk in the last observed five-year period has had a steeper increase, probably related to PSA-testing. In the Nordic countries incidence rates increased in 1993–1997, except in Denmark. In Denmark the incidence rates dropped in 1993–1997, probably as a result of general recommendations not to carry out PSA-testing on healthy men. A similar recommendation was proposed in Norway also. The increase in incidence was most pronounced in Finland, which indicates extensive PSA-testing there. In Finland, the incidence of prostate cancer increased slowly from the 1960s to the beginning of 1990s with age-adjusted incidence per 100,000 men increasing from 22.8 to 39.1. A rapid increase in prostate cancer incidence has been observed since 1991 with age-adjusted incidence per 100,000 men increasing from 43.2 in 1991 to 72.1 in 1997 (Finnish Cancer
Registry, 2000). The annual number of prostate cancer cases is still increasing in Finland. The overall incidence of prostate cancer in the Nordic countries is estimated to double from 1995 to 2020, from about 12000 to almost 24000 new cases, of which half can be attributed to a general ageing in the population (Moller et al. 2002).

Hsing and colleagues (2000) have reviewed recent data on international trends in prostate cancer incidence and mortality. There were large increases too in low-risk countries where there is no screening programme for prostate cancer; 104% in Singapore Chinese, 84% in Miyagi, Japan, 55% in Hong Kong, and 44% in Shanghai, China, between 1975 and 1990. Only in India (Mumbai) does there seem to have been little change in incidence (Michel et al. 1993, Sunny et al. 2004).

### 2.6 Natural history of prostate cancer

Prostate cancer remains one of the most prevalent and least understood of all human malignancies. Pathologic evidence suggests that neoplastic changes of the prostate epithelium begin early in a man's adult life, but do not become clinically evident or relevant until decades later. Some patients live out their lives with a prostate cancer that remains stable for decades without treatment. In other cases, the cancer grows aggressively, responds poorly to therapy, and causes death within a few years. The natural history of this enigmatic disease is heterogeneous, ranging from a benign and indolent course to one that rapidly progresses, causing significant morbidity and mortality (Scardino 2000, Wei and Uzzo 2002).

Prostate cancer is believed to arise from the secretory epithelial cells that line the lumenal surface of the prostate ducts and acini (Ware 1994). Most carcinomas arise in the peripheral zone of the prostate gland (Figure 5), where also the earliest detectable precursor lesion of prostate cancer, prostate intraepithelial neoplasia (PIN), is found (Bostwick and Brawer 1987, Sakr et al. 1993, Ware 1994). The likelihood that an individual PIN lesion progresses into clinical cancer is assumed to be low (Epstein 1994). Another common early lesion is the indolent microscopic prostate cancer. In autopsy studies of prostates of 70–80 year old men who have died from other causes than cancer, microscopic foci of adenocarcinoma are present in more than 50% of the cases (Breslow et al. 1977, Sheldon et al. 1980, Sakr et al. 1993). In most cases, these lesions never progress to clinical cancer in the lifetime of the individual (Gitter 1991). Progression of latent histological cancers to clinically evident tumors seems to be the major rate-limiting step in prostate tumorigenesis.
It is generally accepted that the development of a fully malignant cancer cell requires malignant genetic events, including those that initiate cell transformation as well as those that promote or encourage the transformation process. If histologic cancer represents a step in the development of clinically evident prostate cancer, then the initiation event of prostate cancer appears to occur at approximately the same rate independent of race or place of birth of the individual (Carter et al. 1990). Carter and colleagues (1990) have shown that even though the age-specific prevalence of histological prostate cancer is similar in Japan and the United States, there is marked difference in age-specific prevalence of clinical prostate cancer between Japanese and American men. Therefore, whereas the presence of histologic cancer appears to be related to age, other risk factors that increase the development of prostate cancer probably affect the “promotion” steps of the transformation pathway (Carter et al. 1990).

Clinically detected prostate carcinomas display a variety of phenotypic and malignant potential. Majority of all prostate carcinomas are typical adenocarcinomas, which can be divided into different tumor grades (Gleason 1992). The histological differentiation together with tumor stage, determined by tumor size, as well as the presence of lymph node and distal metastases are used to assess the prognosis of the patients (Gittes 1991). The average 5-year survival of patients with clinically detected prostate cancer is largely dependent on the stage of the tumor at the time of diagnosis and varies from 84% for localized, early stage, low grade disease to 25% for patients with advanced disease (Dickman et al. 1999).
2.7 Prostate cancer screening

Epidemiologically, screening is justified by the importance of the disease and the lack of prospects for primary prevention, but evidence from natural history is unhelpful since men are more likely to die with, rather than from, prostate cancer (Frankel et al. 2003). The aim of screening is to identify cancers that are potentially curable; before a programme can be introduced, it must satisfy the requirement that it does more good than harm, particularly in terms of survival and quality of life. Prostate cancer is a common disease in older men and presents a significant burden to health services. Prostatic tumors range from small slow-growing lesions to aggressive tumors that metastasize rapidly, but because the natural history of prostate cancer is poorly understood, there is controversy about which screen-detected lesions will become clinically significant.

Current methods of screening involve digital rectal examination (DRE), measurement of serum prostate specific antigen (PSA), followed by transrectal ultrasound scanning and biopsy (TRUS), but these lack adequate specificity and sensitivity (Neal and Donovan 2000). Prostate specific antigen (PSA) came into wide use as a prostate detection method in the late 1980s (Stamey et al. 1987, Catalona et al. 1991). The US Food and Drug Administration (FDA) approved the PSA test for the purpose of monitoring disease status of prostate cancer patients in 1986 and for aiding in the detection of the prostate cancer in men above 50 years and older in 1994 (Hankey et al. 1999). The use of PSA test is associated with a substantial increase in the incidence of prostate cancer in men 65 years and older during the late 1980s and early 1990s in the USA (Potosky et al. 1995). In Finland and many other European countries, this increase took place a bit later, in the early and mid 1990s (Auvinen et al. 1996).

Randomized prostate cancer screening studies are ongoing in several countries, including Finland (Schroder et al. 2003, Schroder and Bangma 1997, Maattanen et al. 1999). It is obvious that regular PSA testing of asymptomatic, middle aged men reduces the number of men diagnosed with advanced or metastatic disease. Hakama et al. (2001) concludes that PSA is a valid screening test for prostate cancer, which compares favorably with mammography for breast cancer. However, until an effect on mortality has been shown, routine screening cannot be recommended. It has not yet been established by ongoing randomized controlled PSA screening trials whether mortality of prostate cancer can be reduced by screening (Kramer et al. 1993, Gohagan et al. 1994, Hankey et al. 1999). The decrease in the incidence of the advanced stage disease in the USA since 1991, and the decline in the incidence of the earlier stage disease beginning in 1992 are consistent with
PSA screening effect and give some support to the hopes that testing for PSA may lead to a sustained decline in prostate cancer mortality (Etzioni et al. 1999, Hankey et al. 1999).

There is also some concern that PSA screening leads to the diagnosis of many clinically insignificant (incidental/latent) cancers, which would not cause mortality or even cause symptoms to the patients (Wolf et al. 1996, Saksela 1998). Etzioni et al. (1998) have estimated that 50% of the new prostate cancer cases would not have been clinically diagnosed in the absence of PSA testing. Also there will be false positive screening tests, which will lead to subsequent invasive procedures (Smith et al. 1996). Despite these risks, PSA screening for prostate cancer is recommended by American Cancer Society (von Eschenbach et al. 1997). The rise and fall in prostate cancer mortality observed since the introduction of PSA testing in the general population are consistent with a hypothesis that a fixed percent of the rising and falling pool of recently diagnosed patients who die of other causes may be mislabeled as dying of prostate cancer. The decline in incidence-based mortality (IBM) for distant stage disease and flat IBM trends for localized/regional disease provide some evidence of improved prognosis for screen-detected cases, although alternative interpretations are possible (Feuer et al. 1999). Definitive results regarding usefulness of PSA screening in reduction of prostate cancer mortality will be available only in the future. The available screening tests do not always detect men whose lesions could result in future morbidity or mortality (Frankel et al. 2003).

### 2.8 Concept of risk factors

Most cancers result from the interaction of multiple factors that range from genetic characteristics to personal lifestyle. Researchers who study the causes of cancer use the term *risk factor* to refer to anything that is associated with an increased chance of developing a particular type of cancer. Factors that are associated with a decreased chance of developing a particular cancer are called *protective factors*.

Risk factors or protective factors are a matter of probability. They influence an individual’s odds of developing a disease. That’s not the same thing as actually causing the disease to occur. Some people with one or more risk factors for a particular type of cancer never develop it, while other people who have no known risk factors do develop the disease.

Different cancers have different risk factors. For example, smoking is the most important risk factor (indeed, cause) for lung cancer, but it is not a risk factor for skin
cancer. Conversely, exposure to ultraviolet light from the sun is a risk factor for skin cancer but not for lung cancer. Some risk factors, such as smoking or dietary habits, are modifiable. Individuals may be able to reduce their risk of becoming ill by changing these aspects of their lifestyle. Other risk factors, such as age, gender, ethnic background, or family history of a disease, obviously cannot be modified. To establish the relevance of an imputed risk factor, evidence is sought from epidemiology studies and the ultimate goal of epidemiological studies is to identify risk factors to guide disease prevention strategies (Pienta and Esper 1993).

2.9 Risk factors for prostate cancer

Scientists have investigated a wide variety of factors in an effort to determine whether they might increase or decrease the risk of prostate cancer. The evidence pertaining to most of these factors is not conclusive. Table 2 lists some of the factors currently under investigation, with rankings of the strength of the scientific evidence for each. Factors with a ranking of “3” have been solidly established as risk factors for prostate cancer. The one factor ranked “2+” has nearly achieved the status of fully established, but it is not completely understood. Factors ranked “2,” “2–“, or “1+” have some degree of scientific support, but the evidence in their favor is tentative or conflicting. Factors ranked “1” are not supported by the current scientific evidence (Meister et al. 2002).
Table 2. Ranking of Possible Risk and Protective Factors* for Prostate Cancer Based on the Strength of Scientific Evidence.

<table>
<thead>
<tr>
<th>Risk or Protective Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 50 years</td>
<td>3</td>
</tr>
<tr>
<td>African-American</td>
<td>3</td>
</tr>
<tr>
<td>Family history of prostate cancer</td>
<td>3</td>
</tr>
<tr>
<td>Above-average levels of male hormones (androgens)</td>
<td>2+</td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td>2</td>
</tr>
<tr>
<td>Total dietary fat</td>
<td>2</td>
</tr>
<tr>
<td>Total dietary energy (calories)</td>
<td>2</td>
</tr>
<tr>
<td>Meat</td>
<td>2</td>
</tr>
<tr>
<td>Red meat</td>
<td>2</td>
</tr>
<tr>
<td>Above-average body mass index (BMI)</td>
<td>2-</td>
</tr>
<tr>
<td>Dietary animal fat</td>
<td>2-</td>
</tr>
<tr>
<td>Saturated fat</td>
<td>2-</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>2-</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>2-</td>
</tr>
<tr>
<td>Poultry and fish</td>
<td>2-</td>
</tr>
<tr>
<td>Eggs</td>
<td>2-</td>
</tr>
<tr>
<td>Milk                                     *</td>
<td>2-</td>
</tr>
<tr>
<td>Vitamin A (protective)</td>
<td>2-</td>
</tr>
<tr>
<td>Carotenoids (protective)</td>
<td>2-</td>
</tr>
<tr>
<td>Lycopene (protective)</td>
<td>2-</td>
</tr>
<tr>
<td>Vitamin D (protective)</td>
<td>2-</td>
</tr>
<tr>
<td>Vitamin E (protective)</td>
<td>2-</td>
</tr>
<tr>
<td>Alcohol (protective)</td>
<td>2-</td>
</tr>
<tr>
<td>Alcohol (risk)</td>
<td>2-</td>
</tr>
<tr>
<td>Above-average physical activity (protective)</td>
<td>1+</td>
</tr>
<tr>
<td>Above-average physical activity (risk)</td>
<td>1+</td>
</tr>
<tr>
<td>Above-average lean body mass</td>
<td>1+</td>
</tr>
<tr>
<td>Above-average height</td>
<td>1+</td>
</tr>
<tr>
<td>Above-average number of sexual partners</td>
<td>1+</td>
</tr>
<tr>
<td>History of sexually transmitted disease (gonorrhea or syphilis)</td>
<td>1+</td>
</tr>
<tr>
<td>Human Papilloma Virus (HPV) infection</td>
<td>1+</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>1+</td>
</tr>
<tr>
<td>Cheese/butter</td>
<td>1+</td>
</tr>
<tr>
<td>Phytoestrogens (protective)</td>
<td>1+</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>1+</td>
</tr>
<tr>
<td>Vitamin E (risk)</td>
<td>1</td>
</tr>
<tr>
<td>Above-average endogenous (natural) estrogen level (protective)</td>
<td>1</td>
</tr>
</tbody>
</table>
| * All characteristics listed are risk factors unless they are explicitly identified as protective factors.  

Key:

3 — Established (supported by the scientific evidence)  
2+ — Nearly established, but not fully accepted or fully understood  
2 — Reasonable scientific hypothesis, but lacking solid scientific support  
2- — Speculated, conflicting, or limited scientific support  
1+ — Weak scientific support  
1 — Not supported by the scientific evidence  

Source: American Council on Science and Health (Meister et al. 2002).
2.9.1 Established risk factors

Only a few factors have been conclusively established as risk factors for prostate cancer, and none of them are readily modifiable aspects of a man’s lifestyle. The most obvious established risk factor for prostate cancer is male gender. Age, ethnicity and family history are the other established risk factors.

2.9.1.1 Age

Age is the most important risk factor for prostate cancer. It is well-established that prostate cancer incidence increases dramatically with increasing age. More than any other, this is a cancer of the elderly. About three-quarters of cases worldwide occur in men aged 65 years or more (Parkin et al. 2005). While a very unusual disease in men before age 50, rates increase exponentially thereafter. The registration rate by age cohort in England and Wales increased from 8 (per thousand population) in men 50 to 56 to 68 (per thousand) in men 60 to 64, 260 (per thousand) in men 70 to 74, and peaked at 406 (per thousand) in men 75 to 79. The death rate (per thousand) in 1992 in the 50 to 54, 60 to 64, and 70 to 74 aged cohorts in this same population was 4, 37, and 166, respectively (Middleton et al. 1995). It is one of the most solidly established risk factors for prostate cancer. The risk begins to increase when a man reaches his late forties, and it continues to increase as he grows older. Data from numerous autopsy studies performed in different countries have shown with remarkable consistency an incidence of occult prostate cancer in 15 to 30% of men over the age of 50 (Wynder et al. 1971, Breslow et al. 1977, Guileyardo et al. 1980, Yatani et al. 1982, Yatani et al. 1988, Sakr et al. 1994). By the age of 80 years, as many as 60 to 70% of men have histologic evidence of carcinoma in their prostates (Baron and Angrist 1941, Franks 1954, Andrews 1949, Edwalds et al. 1953). Interestingly, in one autopsy series (Scott et al. 1969), as many as 27% of men in their thirties and 34% in their forties had histologic evidence of unsuspected cancer, suggesting that the pathogenesis of prostate cancer may take decades. The clinical diagnosis of prostate cancer also increases directly with age. From 1991 to 1995, age-adjusted incidence rates of prostate cancer for men under age 65 years was 47.1 per 100,000 men but was 1,217.8 per 100,000 for men 65 years and older (Brawley et al. 2000). Prostate cancer incidence increases with age faster than any other epithelial malignancy.
2.9.1.2 Ethnicity

Being an African-American man is a clearly established risk factor for prostate cancer. They are 69% more likely than white American men to be diagnosed with prostate cancer, and they are more than twice as likely to die from it (Meister et al. 2002). African-American men have a higher incidence of prostate cancer than do black men in Africa or Asia (Meikle and Smith 1988, Waterhouse et al. 1982).

The variation of incidence of prostate cancer in different ethnic groups and emigrants has also given clues to risk factors of prostate cancer. The high rate of prostate cancer from emigrants from Asia (with low incidence of prostate cancer) to the USA (with highest incidence in the world) provides strong evidence in favor of environmental and life style factors as risk factors of prostate cancer (Akazaki and Stemmermann 1973, Kolonel et al. 1988, Shimizu et al. 1991, Cook et al. 1999). On the other hand, high prostate cancer incidence in African Americans has been suggested to be attributable to genetic factors (Irvine et al. 1995).

While men of all racial and ethnic backgrounds are at risk, black men of African descent are at especially high risk. African-Caribbean men, particularly Jamaican men, have the highest rate of prostate cancer in the world (Kleier 2003). Survival is also related to ethnicity with 5-year survivals of whites with localized, regional, or metastatic prostate cancer being 94.7%, 86.6%, and 29.6%, respectively, compared to rates of 87.8%, 69.3%, and 22.7%, respectively, for blacks. African American men are far more likely than other men to die of this disease: 48.7 of every 100,000 African American men die of prostate cancer compared with 19.6 of every 100,000 white men, 14.5 of every 100,000 Hispanic men, 11.3 of every 100,000 American Indian men, and 8.0 of every 100,000 Asian/Pacific Islander men (Figure 6) (Parkin et al. 2001).
Conflicting data have been published regarding the etiology of these outcomes. Historically, African American men have presented at a higher stage and had a worse outcome from the disease than non-African American men. There is an ongoing debate whether this disparity is due to biologic, environmental, or behavioral factors, or a combination of these factors. Furthermore, lack of access to care is implicated (Moul 2000, Optenberg et al. 1995).

2.9.1.3 Family history

Having a family history of prostate cancer in close male relatives is an established risk factor (Meister et al. 2002). A family history of prostate cancer remains an important risk factor for developing the disease (Lesko et al. 1996). Several studies have suggested an increased risk in male relatives of men with prostate cancer (Bauer et al. 1998, Cerhan et al. 1999, Bratt et al. 1999, Kupelian et al. 1997a, Walsh and Partin 1997, Whittemore et al. 1995). First-degree relatives (brother, father) of men with prostate cancer have a two- to three-fold increased risk of developing prostate cancer compared to the general population (Steinberg et al. 1990, Cerhan et al. 1999). It has been estimated that approximately 9% of all prostate cancers may result from heritable susceptibility genes (Gronberg et al. 1997). Several authors have completed segregation analyses, and although a single, rare autosomal gene has been suggested to cause cancer in some of these families, the burden of evidence suggests that the inheritance is considerably more complex (Schaid et al. 1998). Further
study has demonstrated that, controlling for all other tumor variables, treatment of the primary tumor is more likely to fail in men with a family history of prostate cancer (Kupelien et al. 1997b). This risk factor may reflect a combination of inherited characteristics and common life styles shared by family members. It is believed that approximately 9% of all prostate cancer cases result from genetic mutations and that as many as half of all prostate cancer cases in younger men may result from inherited conditions. This risk may increase up to 10-fold if three or more relatives are affected (Steinberg et al. 1990). It has been estimated that about 5 to 10% of all and 40% of early-onset cancers (i.e., age at diagnosis less than 50 years old) are hereditary (Walsh and Partin 1997). The evidence specifically linking genetic predisposition to prostate cancer risk is not as strong as the evidence for family history.

Interestingly, the presence of breast or ovarian cancer in a mother or sister was also positively associated with prostate cancer risk, although the relative risk was lower, at 1.7. Men with a family history of both prostate and breast or ovarian cancer had an even higher relative risk of developing prostate cancer (5.8). Whether the association with breast or ovarian cancer reflects genetic linkage or simply similar environmental or dietary exposures remains to be determined (Small and Reeze 2000).

2.9.2 Other proposed risk factors

2.9.2.1 Vasectomy

Vasectomy is the safest method of male sterilization (Schwingl and Guess 2000). It has become an increasingly common procedure in many countries since the early 1970s. Worldwide about 42 to 60 million couples rely on vasectomy for contraception (Population Information Program 1992). In India, vasectomy has been practiced since the 1950s following ongoing promotion by the National Family Planning Programme (Population Research Centre (PRC) Punjab University, Chandigarh and International Institute for Population Sciences (IIPS) 1995, Thakore and Patel 1972, Choudhuri 1975). It is estimated that 13 million Indian men have had a vasectomy and that 7% of all married couples in the reproductive age group use vasectomy as a method of contraception. The majority of these men underwent the procedure by the late 1970s and now are entering the age range of greatest prostate cancer risk (Tripathy et al. 1994).
The possibility of a relationship between vasectomy and prostate cancer was initially raised with the publication of two retrospective epidemiology studies by Rosenberg and Mettlin et al in 1990 (Rosenberg et al. 1990, Mettlin et al. 1990). After these two articles were published, a panel of experts gathered at the World Health Organisation in Geneva to discuss the hypothesis that men who had a vasectomy have an increased risk of prostate cancer. The unanimous consensus of this group was that the available data did not suggest a link but that additional research should be conducted. In 1993, Giovannucci et al (1993c) published a retrospective analysis of the possible relationship between vasectomy and prostate cancer which raised significant concern in the scientific community and the media. The editorial published in the same issue of the Journal of the American Medical Association pointed out the problems in the study of Giovannucci et al, emphasizing that they were not at all conclusive and again suggested that additional research was needed (Howards and Peterson 1993).

The analysis of a further set of cases and controls from one of the earlier conducted hospital-based surveillance systems by Rosenberg et al. (1994) found no significant association, suggesting that the earlier finding was due to chance. Reviews of these and other early studies concluded that vasectomy was probably not a risk factor for prostate cancer (Guess 1990, Skegg 1993). Moreover, a biological explanation of any association seemed unlikely (Howard 1993).

Indeed, many recent studies showed no increased risk (Zhu et al. 1996, Deantoni et al. 1997, Bernaldelgado et al. 1998), and have failed to find a link between vasectomy and prostate cancer. Scientists have been unable to identify a biologically plausible reason for vasectomy to increase a man’s cancer risk. The idea that there is an association between vasectomy and any true increase in prostate cancer risk has only weak scientific support. Although the evidence was inconsistent, sufficient concern arose for many urologists to screen vasectomized men early for prostate cancer and to discourage vasectomy in men with a strong family history of prostate cancer (Sandlow and Kreder 1996).

Several studies looking at a possible connection between vasectomy and prostate cancer are currently under way. The largest of these studies is the NCIs Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which began in 1992. The PLCO Trial is evaluating screening procedures for prostate cancer and will prospectively examine potential risk factors, including vasectomy, associated with prostate cancer. The PLCO is a long-term study; results are expected by 2015 (Meister et al. 2002).
2.9.2.2 Sexual history

Several studies have attempted to relate various aspects of a man’s sexual history, such as above-average number of sex partners or history of sexually transmitted diseases, to prostate cancer risk (Pienta and Esper 1993, Newell et al. 1987, Talamini et al. 1986, Steele et al. 1971). An association between total testosterone levels and sexual activity has been suggested in some studies (Bosland 2000). Some studies have found that these sexual factors predict an increased risk of prostate cancer, but the findings are questionable because of problems with study design. In many of the studies, the data were collected by asking elderly men with and without prostate cancer about sexual events that occurred decades in the past. Men who have been diagnosed with a disease that can affect their sexual functioning, such as prostate cancer, may recall past sexual events differently than healthy men do. These differences in recall could distort the results of a study.

In a recent case control study (Giles et al. 2003) conducted in Australia, there was no association of prostate cancer with the number of sexual partners or with the maximum number of ejaculations in 24 h. Men who averaged five or more ejaculations weekly in their 20s had an odds ratio of 0.66 (0.49–0.87) compared with those who ejaculated less often. The null association with the number of sexual partners argues against infection as a cause of prostate cancer in this population. Ejaculatory frequency, especially in early adult life, is negatively associated with the risk of prostate cancer, and thus the molecular biological consequences of suppressed or diminished ejaculation are worthy of future research.

2.9.2.3 Dietary factors

Diet has been implicated in prostate cancer risk. People in countries such as China and Japan are far less likely than Westerners to develop prostate cancer. Notably, when people migrate to the US, their rates of prostate cancer rise greatly and, since their genetic make-up is the same, there appears to be something about living in America that increases these men's chances of developing prostate cancer. Diet is the number one suspect.

An interesting observation is that although the incidence of latent (occult, histologically evident) prostate cancer is similar throughout the world, clinical prostate cancer varies from country to country by as much as 20-fold (Wynder et al. 1971). Previous
Ecologic studies have demonstrated a direct relationship between a country's prostate cancer-specific mortality rate and average total calories from fat consumed by the country's population (Armstrong and Doll 1975, Rose and Connolly 1992). Studies of immigrants from Japan have demonstrated that native Japanese have the lowest risk of clinical prostate cancer, first generation Japanese-Americans have an intermediate risk, and subsequent generations have a risk comparable to the U.S. population (Haenszel and Kurihara 1968, Shimizu et al. 1991). Animal models of explanted human prostate cancer have demonstrated decreased tumor growth rates in animals fed a low-fat diet (Wang et al. 1995, Connolly et al. 1997).

Increased dietary intake of fruits and vegetables has been associated with a reduced risk of prostate cancer in some studies. One study evaluated 1619 prostate cancer cases and 1618 controls in a multicenter, multi-ethnic population. The study found that intake of legumes, yellow-orange, and cruciferous vegetables were associated with a lower risk of prostate cancer (Kolenel et al. 2000).

Another significant difference between Asian and Western diets is the average amount of soy protein consumption, which averages 35 grams/day in Taiwan (Yip et al. 1999). There is current interest in the possibility that the low risk of prostate cancer in certain Asian populations may result from their high intake of soy products (Miller et al. 1993). Soya beans are widely known for their possible anti-cancer potential, and the latest discoveries are encouraging. It has been found that the beans, which contain compounds called isoflavanoids, can actually inhibit prostate cancer cell growth in the laboratory (Miller et al. 1993). Soya protein can be found in many foods such as tofu, soya milk and yoghurt. The Eastern diet is based around soya proteins as an alternative to meat. In one study, Japanese men in Hawaii who consumed tofu approximately once per day, were 65 per cent less likely to develop prostate cancer in comparison with men eating tofu less than once in a week (Severson et al. 1989). In another study, Seventh-day Adventist men in California who consumed soy milk more than once daily were 70% less likely to develop prostate cancer as men who did not consume soy milk (Jacobsen et al. 1998). The pronounced protective effects of soy consumption in these studies is striking. Further work needs to be done to understand its effects on prostate cancer growth and role as dietary inhibitor of prostate cancer development and growth.

Micronutrients in the diet have also been implicated in the pathogenesis of prostate cancer (Platz et al. 1999, Nomura et al. 1997, Hsing et al. 1990a). Many studies showed that men with the highest level of selenium had one-third the risk of developing prostate cancer compared with men with the lowest selenium levels (Heinonen et al. 1998, Clark et
One of the richest sources of selenium is brazil nuts. Selenium is also found in sunflower seeds, wholewheat bread, avocados and lentils and has been shown to reduce the incidence of prostate cancer. The association between prostate cancer and baseline vitamin E and selenium was evaluated in the trial-based cohort of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC). There were no significant associations between baseline serum alpha-tocopherol, dietary vitamin E, or selenium and prostate cancer overall. The associations between prostate cancer and vitamin E and some of the baseline dietary tocopherols differed significantly by alpha-tocopherol intervention status, with the suggestion of a protective effect for total vitamin E among those who received the alpha-tocopherol intervention (Hartman et al. 1998b).

Vitamin D inhibits the development and growth of prostate cancer cells. Epidemiologic results on serum vitamin D levels and prostate cancer risk have, however, been inconsistent. Some studies suggest that higher serum vitamin D levels may reduce the risk of prostate cancer (Blutt and Weigel 1999). Schwartz and Hulka (1990) showed a relationship with known risk factors for prostate cancer, including age, race, and living in northern latitudes, which were associated with low serum levels of vitamin D. Others have shown that low serum vitamin D levels correlate with an increased risk of palpable and high-grade tumors. A further link between high dietary calcium intake and prostate cancer risk has been shown, suggesting that chronically high calcium intake might confer risk by causing lower endogenous vitamin D levels (Giovannucci et al. 1998b). In a recent longitudinal nested case-control study conducted on Nordic men (Norway, Finland and Sweden) using serum banks of 200,000 samples, it was recommended that vitamin D deficiency be supplemented, but too high vitamin D serum level might also enhance cancer development (Tuohimaa et al. 2004).

A variety of carotenoids, including lycopene, inhibit prostate cancer cells in vitro (Yip et al. 1999). A higher intake of lycopenes, the agent in tomatoes and beets that gives them their red color, has been shown to decrease risk of prostate cancer (Gann et al. 1999). In a large study of food intake and risk of prostate cancer, Giovannucci and colleagues (1995) demonstrated an inverse relationship between consumption of lycopenes and the risk of prostate cancer. The major dietary sources of lycopenes are cooked tomatoes, tomato juice, and paste. The role of vitamin A in prostate cancer growth is less established (Reichman et al. 1990). Several randomized trials are ongoing evaluating the role of nutrition in preventing prostate cancer progression, but these results will not be available for several years.
Consumption of fatty fish might reduce the risk of prostate cancer, although epidemiological studies of fish consumption are rare. Many studies have found that a high level of Omega-3 fatty acids in the body was associated with a reduced risk with prostate cancer (Terry et al. 2001, Norrish et al. 1999). Oily fish such as salmon, trout, tuna, mackerel and herring are rich in healthy fats known as Omega-3 fatty acids. In two recent studies it was found that men with high consumption of fish had a lower risk of prostate cancer, especially for metastatic cancer (Augustsson et al. 2003, Terry et al. 2003). Marine fatty acids may account for part of the effect, but other factors in fish may also play a role.

2.9.2.4 Non alcoholic beverages

Geographic variation in incidence rates of clinically evident prostate cancer suggests that it is caused by exogenous factors (Yatani et al. 1982). While the epidemiologic evidence implicating tobacco and alcohol is inconsistent (Colditz 1996, Breslow and Weed 1998), biological evidence suggests that non-alcoholic beverages could be involved. Both coffee and tea are mutagenic (Nagao et al. 1979), subcutaneously injected tannic acid is carcinogenic in rodents (IARC 1975), and some carbonated beverages contain methylglyoxal, a genotoxin (IARC 1991). However, in vitro experiments suggest that components of tea could interfere with the development of prostate cancer (Ren et al. 2000). Thus, some data indicate that coffee and tea consumption could initiate cancer on the one hand, and that tea consumption could prevent prostate cancer on the other. However, because of limited assessment of these exposures in epidemiologic studies, the human evidence remains inconclusive (Blot et al. 1996).

2.9.2.5 Alcohol and tobacco

In the 1960s, it was suggested that heavy consumption of alcohol might reduce the risk of prostate cancer, perhaps by lowering male hormone (androgen) levels in the body. A biologically plausible protective role for alcohol in prostate carcinogenesis has been hypothesised from reports that alcohol may increase metabolic clearance of testosterone (Gordon et al. 1976). More recently, it has been suggested that heavy intake of alcohol might increase prostate cancer risk by interfering with nutrition or by reducing the ability of the liver to detoxify cancer-causing agents. A large population-based case-control study
reported evidence of a dose-response relation between alcoholic beverage consumption and risk of prostate cancer (Hayes et al. 1996). While the epidemiological literature generally does not support a relation (Breslow and Weed 1998), the common occurrence of this cancer coupled with the routine use of alcohol in many populations means that even a moderate effect may be of public health significance. In another recent epidemiologic study, a positive association was found between moderate alcohol consumption and the risk of prostate cancer. Liquor, but not wine or beer, consumption was positively associated with prostate cancer (Sesso et al. 2001). However, there is little evidence to support either of these ideas. Investigations of the relationship of alcohol intake to prostate cancer risk are continuing.

Because tobacco smoking is an established risk factor for a wide variety of cancers, researchers have considered the possibility that it may be linked with prostate cancer as well. However, the evidence for such an association is weak at best. Most studies have found no important difference in prostate cancer rates between smokers and nonsmokers or have shown only a small excess of prostate cancers among smokers. Hsing and co-workers (1990a) observed an increased relative risk of prostate cancer for cigarette smoking (OR 1.8) and for chewing tobacco (OR 2.1). Coughlin and colleagues (1996) observed in their study that the risk of developing prostate cancer was 1.21 to 1.45-fold increased among men with a history of smoking. However, compared to its very strong impact on carcinogenesis of other organs, it appears that cigarette smoking adds little, if any, to the risk of developing prostate cancer (Lumey 1996). Any small excess could easily be attributable to increased diagnosis of latent prostate cancers among smokers. Because smokers tend to have more health problems than nonsmokers do, they go to the doctor more often and therefore may be more likely to be tested for prostate cancer.

2.9.2.6 Male hormones (Androgens)

The development of the prostate is dependent upon the secretion of testosterone by the fetal testis. The prostate gland is part of the male reproductive system, and its normal growth and function are regulated by male sex hormones (androgens). Thus, it’s logical to suspect that androgens (testosterone and related substances) might have some effect on the risk of prostate cancer. Scientists have been investigating the possible role of androgens in prostate cancer since the 1970s, and the results of their studies have been reasonably consistent. It now seems certain that androgens do play some role in the causation of prostate cancer, and
that having higher than average levels of androgens in the body probably increases risk (Meister et al. 2002).

Androgens stimulate prostate cancer in vitro and in vivo. Androgen levels generally parallel prostate cancer risk in various populations of men. Although there are conflicting data, a number of studies have demonstrated that levels of testosterone and, especially dihydrotestosterone, are highest in black males, of intermediate levels in white males, and lowest in native Japanese (Ellis 1992, Rose Connolly 1992, Wu et al. 1995). The risks for prostate cancer in these ethnic groups directly parallel these androgen levels. Differences in androgen levels may explain at least part of the variation in prostate cancer rates among ethnic groups. Several studies have shown that androgen levels in African-American men tend to be higher than those in men of other ethnic groups. This may partially explain the high susceptibility of African-American men to prostate cancer. Effects on androgens might also be a mechanism by which some lifestyle factors could influence prostate cancer risk. For example, changes in dietary habits may lead to changes in androgen levels and thus perhaps to changes in prostate cancer risk (Meister et al. 2002). Androgen deprivation in almost all forms leads to involution of the prostate, a fall in PSA levels, apoptosis of prostate cancer and epithelial cells, as well as a clinical response in prostate cancer patients (Peters and Walsh 1987).

In a recent case control study nested in cohorts in Finland, Norway and Sweden, to investigate the association of serum levels of testosterone, the principal androgen in circulation, and sex hormone-binding globulin (SHBG) with risk, no support was found for the hypothesis that high levels of circulating androgens stimulate development and growth of prostate cancer (Stattin et al. 2004).

2.9.2.7 Body size

Obesity is a growing problem in contemporary societies, due to the rapid adoption of a modernized lifestyle that results in increased carbohydrate and fat-rich dietary intake, reduced physical activity and extended life expectancy. It has been speculated that larger men, those who are heavier, taller, or both, may be at increased risk of prostate cancer. Men with high bone mass may be at an increased risk of prostate cancer. Although the biological mechanisms underlying this relation are not understood, cumulative exposure to high levels of androgen, insulin-like growth factor 1, or calcium intake may be involved (Zhang et al. 2002).
Most studies of body size have focused on body mass index (BMI), a measure that incorporates both weight and height (Abu-Abid et al. 2002). High BMI is indicative of obesity. It is often associated with high calorie intake and low physical activity, both of which are also being investigated as possible prostate cancer risk factors. Some studies have found higher prostate cancer rates among men with high BMI, but a larger number have found no such relationship. A few indicated that taller or larger men might be at higher risk.

Increasing BMI is associated with decreasing levels of total serum testosterone (Field et al. 1994, Dai et al. 1981). Testosterone has been shown to act as a promoter of prostate cancer in an animal model, (Pollard and Luckert 1987) and higher total testosterone levels in men are associated with increased risks of prostate cancer (Gann et al. 1996). Small changes in hormone levels might cause large changes in risk (Hsing 1996). This relation may partly explain why the risk of prostate cancer was lower among non smokers with high BMI than among non smokers with low BMI. Evidence of an increased BMI as a risk factor for prostate cancer is controversial (Kolonel 1996). A positive association between prostate cancer risk and muscle mass, but not fat mass, has been observed (Severson et al. 1988). This may suggest exposure to endogenous or exogenous androgenic hormones or other anabolic factors (Bosland 2000).

2.9.2.8 Physical Activity

Physical activity has marked effects on many functions of the human body, which may influence overall cancer risk (Kujala et al. 1996). These effects include direct mechanical processes such as improved circulation, ventilation and bowel transit time, improved energy balance and immune function, and possibly the capacity to perform DNA repair.

There are studies suggesting that the level of physical activity may be a possible risk factor for prostate cancer, but the evidence for such an association is inconclusive (Andersson et al. 1997). Exercise may decrease or increase circulating androgen concentrations or have no effect, depending on the type of exercise and time of sampling. The hormonal influences may mediate the effect of exercise (Bosland. 2000). Many studies conducted in North America, Asia, and Europe (Andersson et al. 1995, Giovannucci et al. 1998a, Hartman et al. 1998a, Wannamethee et al. 2001) demonstrated that either occupational physical activity (OPA) or leisure time physical activity (LPA), or both activities combined, significantly decreased prostate cancer risk by 10–70%. However,
some other studies observed a significantly increased risk among physically active men (Le Marchand et al. 1991, Ilic et al. 1996), while still other studies found no evidence of any effect (Norman et al. 2002). These studies related to prostate cancer are hampered by variation in detection of latent disease. Thus, there is currently little support for the concept that physical activity either increases or decreases prostate cancer risk (Lacey et al. 2001).

2.9.2.9 Benign prostatic hyperplasia

Evidence that patients with history of benign prostatic hyperplasia have a higher risk for prostate cancer has been suggested in some studies (Armenian et al. 1974, Greenwald et al. 1974, Bosland 2000). An association between prostate cancer risk and prior occurrence of benign prostatic hyperplasia is biologically unlikely. Although both diseases appear to be androgen dependent, benign prostatic hyperplasia arises most often in the central or transitional zone of the prostate, whereas more than 80% of all cancers develop in the peripheral zone of the prostate gland.
3. PILOT STUDY

This pilot case control study was conducted by our Bombay Population Based Cancer Registry, Mumbai India in collaboration with the Harvard School of Public Health, Boston, USA in the year 1996 to study the association of vasectomy with prostate cancer. This was a hospital based case control study consisting of 175 prostate cancer cases and 978 controls with cancer diagnosis other than prostate cancer. It was conducted at hospitals covered by the Bombay Population Based Cancer Registry at Mumbai, India (Platz et al. 1997). Cases were all patients having age more than 40 years with newly diagnosed prostate cancer admitted to Tata Memorial Hospital or to any other hospital in Mumbai covered by the Bombay Population Based Cancer Registry between 1st July, 1993 and 30th June, 1994. Controls were all male patients with newly diagnosed cancer of the oesophagus (31.9%); larynx (26.8%); lip, oral cavity, or pharynx (22.6%); or colon, rectum, or anus (18.7%) admitted to the same hospital over the same time period as the cases and satisfying the same age and residency requirements. History of vasectomy, demographic, and lifestyle factors were obtained by structured interview. Multiple logistic regression was used to estimate odds ratios (OR) with 95% confidence intervals (CI).

From the results it was observed that 8.7% of the cases and 8.3% of the controls had had a vasectomy. The odds ratio for prostate cancer comparing men who had had a vasectomy to those who did not was 1.48 (95% CI: 0.80–2.72) controlling for age at diagnosis, smoking status, alcohol drinking, and other demographic and lifestyle factors. Risk of prostate cancer associated with vasectomy appeared to be higher among men who underwent vasectomy at least two decades prior to cancer diagnosis or who were at least 40 years old at vasectomy.

There are several strengths to this study. Cases and controls were drawn from a population in India where screening for prostate cancer was not customary and most cases were symptomatic at diagnosis. As part of an Indian government programme to curtail fertility during the 1960s and 1970s vasectomies were performed in specially dedicated clinics and camps with incentives (Population Research Centre (PRC) Punjab University, Chandigarh and International Institute for Population Sciences (IIPS) 1995, Thakore and
Patel 1972, Choudhuri 1975), thus the distribution of unidentified socio economic or behavioral risk factors for prostate cancer between men with and without vasectomy is likely to be quite different in this population than in the previously studied western countries. In addition to technical convenience, use of cancer patients as the comparison likely diminished biased recall as both cases and controls were hospitalized with a similar and serious disease.

Although not statistically significant, the results of this hospital based case control study are consistent with the hypothesis of a positive association between vasectomy and prostate cancer.

As vasectomy is a common method of family planning in India and worldwide, its health consequences in general and any risk for development of prostate cancer in particular, needs to be studied. The finding of this hospital based study as well as a review of the previous epidemiological studies on prostate cancer world wide enabled for formulating a working hypothesis for the present study.
4. OBJECTIVES OF THIS STUDY

The objectives of this study were to find out the etiological factors for prostate cancer from a low risk population of a developing country. The specific aims were to assess the role of the following risk/protective factors:

1. vasectomy
2. marital history
3. dietary habits
4. tobacco habits
5. alcohol habits
5. MATERIAL AND METHODS

5.1 A demographic profile of the study area, Mumbai

This study was conducted at Bombay Population Based Cancer Registry (PBCR), located at Mumbai, which is the capital of the state of Maharashtra. The Bombay PBCR is the first Population Based Cancer Registry established in India in June 1963, as a unit of the Indian Cancer Society, at Mumbai, with the aim of obtaining reliable morbidity and mortality data on cancer from a precisely defined urban population (Greater Mumbai). For the past four decades, this registry has been collecting all essential information pertaining to cancer patients, in the resident population of Greater Mumbai. During the period 1964–2002 a total of 250,000 new cancer cases (all sites) and 130,000 cancer deaths (all sites) were registered from the residents of Mumbai (12 million inhabitants).

In India, a population census is undertaken every ten years, the last one being in 2001. The population of Greater Mumbai as per the 2001 census (on 1st March) was 11,914,398, with a sex ratio of 811 females per 1000 males and having a density of 19,760 inhabitants per sq.km., confirming the fact that it is the most heavily populated district in Maharashtra State. The decennial growth rate of the population between 1991 and 2001 was of the order of 20.2%. The literacy rate was found to be 87.0% in 2001.

Greater Mumbai is the industrial heart of India and has a multi-religious, multi-lingual population, representing every state in the Union, approximately 68.0% being Hindus, 16.8% Muslims, 4.5% Christians (mostly Hindu converts), 5.6% Neo-Buddhists, 3.6% Jains (an ultra-conservative Hindu sect.), 0.8% Parsis (Zoroastrians) and 0.5% Sikhs.

The majority of hospitals in the city are maintained by the Municipal Corporation and the State Government, which are basically responsible for conducting Public Health and Medical Services in the city. The diagnosis and treatment of cancer are centralized, being undertaken only by certain hospitals in Mumbai. Major cancer surgery however, is undertaken at all the major hospitals in town, as well as in some of the well-equipped nursing homes in the city.
For the convenience of civic administration and census operation, Greater Mumbai is divided into 15 wards, which are further sub-divided into 88 sections. Currently, the city functions as the administrative Capital of Maharashtra State.

Greater Mumbai is in fact an island, joined to the mainland by a number of bridges. It has a warm and humid climate, the period from November to February being comparatively cooler when the temperature ranges between 20\(^\circ\) and 28\(^\circ\) C. From the month of March onwards, the weather starts getting warmer. April to June is hot, the temperature often touching 35\(^\circ\) C during day time. The rains start by mid-June and continue through July, August and September. The average annual rainfall is 2500 mms.

5.2 Study design

This study was planned and conducted as a matched case-control study. The cases were all prostate cancer patients registered by the Bombay Population Based Cancer Registry during the period, 1\(^{st}\) January 1998 to 31\(^{st}\) December 2000. Cases who had a microscopic proof of diagnosis were included in the study. The controls were healthy men belonging to the resident general population of Mumbai, India. Two controls for each case matched by age and place of residence were selected as the comparison group. Two controls were elected for each case to ensure enough power for the study. The controls were elected from the neighborhood of each case aiming at a maximum age difference of +5 years between the members of the case-control triplet. In a cosmopolitan city like Mumbai, neighborhood is defined as either in the same building, or in the same residential complex or in the same locality where the case reside.

5.3 Selection of cases and controls

During the period 1998 to 2000, a total of 766 prostate cancer cases were registered by the Bombay PBCR. Out of these, 172 (22.5%) cases that were not having any microscopic proof of diagnosis were excluded from this study. An attempt had been made to interview all the 594 (77.5%) cases with microscopic proof of diagnosis and their respective age matched controls.
Controls who had a past history of urological disease or had undergone surgery for benign prostatic hyperplasia (BPH) of the prostate have been excluded from the study. These questions were raised before conducting an interview and only eligible controls were interviewed.

5.4 Preparation of the questionnaire

Keeping the objectives of this study as the guidelines, a questionnaire was prepared for data collection. The questionnaire consisted of the following sections,

1. Identification particulars
2. Socio-demographic parameters
3. History of vasectomy
4. General dietary patterns
5. Tobacco and alcohol habits

The questions were constructed by an expert committee that consisted of clinicians and epidemiologists.

5.5 Data collection

One trained male social investigator was appointed to collect the exposure history of the cases and controls. An appeal letter signed by the principal investigator of our organization was provided in order for a permission to interview the cases and controls. The interview has been carried out for all eligible cases and respective controls from 1st November, 1999 to 30th October 2001. After interviewing a case, all efforts were made to interview simultaneously two controls. For those cases having a single control or no controls, a second and third visit was made within a week time in order to find out respective controls.

To collect the exposure history of cases who already died before an interview has been made by interviewing the nearest relative of the patient, that is, either wife or son or male sibling. Over 95% of the proxy respondents were either wife or son or male sibling and 5% were others.
Although all efforts have been made to interview all the 594 microscopically proved cases and respective age matched controls, two controls for each case, only 390 cases (65.7%) with two controls for each case were available and were included in the study for final analysis. The reasons for excluding the remaining 204 cases (34.3%) were due to migration, door closed, not willing to give personal details, too old / died and proxy respondents were not available or not cooperative to complete the interview, no controls were interviewed, controls were not willing to give personal details etc. Only full triplets were available for the analysis. Among the 390 cases included in the final analysis, 142 cases were estimated to have the time of death before the time of interview. Therefore the information was received by proxy respondents. In another 14 cases the interview was known to be based on proxy respondents mainly because of advanced disease and severe condition of the patient. The information for a total of 156 (40.0%) cases was therefore known to be collected by proxy respondents. For the remaining 234 (60.0%) cases, information was reported by self. For all the 780 controls included in the final analysis, information was reported by self. Masking of the investigator for data collection could not be ensured although the objectives/hypothesis of the study was not made known to him.

For some of the cases, it was not possible to find the proper age matched controls residing in the neighborhood of the respective cases due to less number of old age men in the general population of Mumbai. More than 60% of the age matched case-control triplets included in the study for final analysis had an age difference of more than ±5 years between the case-control pairs or triplets, mainly because the neighborhood controls were younger than the cases. Hence a failure in age matching occurred.

The data collected by the social investigator was compiled and quality checks were carried out. Cross checks were also performed for consistency of the information collected. Variable value range checks were also carried out.

5.6 Data analysis

Data were entered in EPI6 and range checks were carried out after completion of data entry. One way and multi-way frequency tables were generated using EPI6 and Stata 7.0 package.

Due to failure in age matching, unconditional logistic regression method was used for risk estimates. For the purpose of evaluating the extent of failure to match for age, conditional logistic regression analysis was also carried out for those variables which
remained statistically significant in the unconditional multivariate model. The details of the methods were taken from Breslow and Day (1980).

First univariate analysis was performed and odds ratios (OR) with 95 per cent confidence interval (95% CI) were estimated for each main exposure and its various components. For example, if ‘vasectomy’ is the main exposure, then we considered ‘age at vasectomy’ and ‘time since vasectomy’ as its components.

Table 3 represents the list of all main variables in the study and their stratified components.

**Table 3. The list of all main variables and their stratified components included in the analysis**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>agg</td>
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<tr>
<td>Age at marriage</td>
<td>am1g</td>
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<tr>
<td>Vasectomy</td>
<td>vst1</td>
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<tr>
<td>Age at vasectomy</td>
<td>vst2g</td>
</tr>
<tr>
<td>Time since vasectomy</td>
<td>vst3g</td>
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<tr>
<td>Summary of fruits and vegetables consumption</td>
<td>svfg</td>
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<tr>
<td>Summary of fish eating</td>
<td>fishg</td>
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<tr>
<td>Summary of meat consumption</td>
<td>meatg</td>
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<tr>
<td>Coffee drinking</td>
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<tr>
<td>Tea drinking</td>
<td>teag</td>
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<tr>
<td>Oil/fat consumption</td>
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<tr>
<td>Smoking habits</td>
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<tr>
<td>Bidi smoking habits</td>
<td>bd1</td>
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<tr>
<td>Number of bidi smoked</td>
<td>bd2g</td>
</tr>
<tr>
<td>Time since start of bidi smoking</td>
<td>bd5g</td>
</tr>
<tr>
<td>Cigarette smoking habits</td>
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<tr>
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<tr>
<td>Tobacco chewing</td>
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<tr>
<td>Number of times chewed</td>
<td>pma2g</td>
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<tr>
<td>Time since start of tobacco chewing</td>
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<tr>
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<td>Time since start of whisky drinking</td>
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<tr>
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</tr>
<tr>
<td>Quantity of toddy drank</td>
<td>todb2g</td>
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<tr>
<td>Time since start of toddy drinking</td>
<td>todb6g</td>
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</table>
In order to observe for the correlation of each main exposure with other main exposures in the study and the influence of highly correlated factors on the results obtained, a correlation matrix was also constructed (table 4). A correlation coefficient of more than 0.5 indicates a high correlation between those variables.

**Table 4.** The correlation matrix for all the main exposures in the present study

<table>
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<tr>
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<th>svfg</th>
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<th>meatg</th>
<th>teag</th>
<th>cofeg</th>
<th>o1g</th>
<th>smok</th>
<th>bd1</th>
<th>cg1</th>
<th>pma1</th>
<th>alco</th>
<th>winb1</th>
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<tr>
<td>o1g</td>
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<td>-0.03</td>
<td>0.01</td>
<td>-0.02</td>
<td>-0.03</td>
<td>0.08</td>
<td>-0.03</td>
<td>1.00</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>smok</td>
<td>-0.06</td>
<td>-0.05</td>
<td>0.04</td>
<td>-0.01</td>
<td>0.06</td>
<td>0.12</td>
<td>0.03</td>
<td>0.04</td>
<td>-0.01</td>
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<tr>
<td>bd1</td>
<td>-0.01</td>
<td>0.05</td>
<td>-0.01</td>
<td>0.03</td>
<td>0.02</td>
<td>0.04</td>
<td>0.07</td>
<td>-0.03</td>
<td>0.01</td>
<td>0.15</td>
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<td>cg1</td>
<td>-0.04</td>
<td>-0.07</td>
<td>0.05</td>
<td>-0.03</td>
<td>0.04</td>
<td>0.08</td>
<td>-0.02</td>
<td>0.06</td>
<td>-0.02</td>
<td>0.78</td>
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<td>pma1</td>
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<td>-0.12</td>
<td>-0.05</td>
<td>0.04</td>
<td>-0.02</td>
<td>-0.02</td>
<td>-0.03</td>
<td>-0.05</td>
<td>0.03</td>
<td>-0.26</td>
<td>-0.01</td>
<td>-0.22</td>
<td>1.00</td>
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<tr>
<td>alco</td>
<td>-0.08</td>
<td>-0.21</td>
<td>0.04</td>
<td>-0.03</td>
<td>0.20</td>
<td>0.22</td>
<td>-0.01</td>
<td>0.09</td>
<td>0.01</td>
<td>0.31</td>
<td>0.00</td>
<td>0.27</td>
<td>-0.06</td>
<td>1.00</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>winb1</td>
<td>-0.09</td>
<td>-0.10</td>
<td>-0.01</td>
<td>0.07</td>
<td>0.16</td>
<td>0.13</td>
<td>-0.02</td>
<td>-0.03</td>
<td>0.00</td>
<td>-0.02</td>
<td>0.08</td>
<td>-0.06</td>
<td>0.09</td>
<td>0.23</td>
<td>1.00</td>
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</tr>
<tr>
<td>wsk1</td>
<td>0.01</td>
<td>-0.08</td>
<td>0.05</td>
<td>-0.08</td>
<td>0.04</td>
<td>0.07</td>
<td>0.00</td>
<td>0.09</td>
<td>0.01</td>
<td>0.26</td>
<td>-0.07</td>
<td>0.27</td>
<td>-0.12</td>
<td>0.60</td>
<td>-0.62</td>
<td>1.00</td>
<td></td>
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<tr>
<td>todb1</td>
<td>0.06</td>
<td>0.01</td>
<td>0.00</td>
<td>-0.04</td>
<td>0.08</td>
<td>0.07</td>
<td>-0.01</td>
<td>0.11</td>
<td>0.03</td>
<td>0.07</td>
<td>-0.01</td>
<td>0.07</td>
<td>0.05</td>
<td>0.11</td>
<td>-0.01</td>
<td>0.09</td>
<td>1.00</td>
</tr>
</tbody>
</table>
It can be observed from table 4 that the variables meat consumption (meatg) and fish consumption (fishg) had a correlation coefficient of 0.70, indicating that these two were highly correlated and so most of the cases and controls who consumed fish were also meat consumers. In the common vegetarian diet in India, neither fish nor meat is included. The variables smoking (smok) and cigarette smoking (cg1) had a correlation coefficient of 0.78, suggesting that most of the smokers were cigarette smokers. Also alcohol (alco) and whisky drinking (wsk1) habits had a correlation of 0.60, suggesting that most of the alcohol drinkers were coded as whisky drinkers. But whisky drinking and wine drinking (winb1) had shown a negative correlation in this study.

The multiple logistic regression method was employed to estimate the adjusted odds ratios for each main exposure and its various components with 95% CI. Since the etiology of prostate cancer is largely unknown, the adjusted odds ratios for each exposure under study were obtained by adjusting with age (both in unmatched and matched design) and with all other main exposures which showed statistical significance in the univariate analysis. The main variables included in the original multivariate model were age (ageg), age at marriage (am1g), vasectomy (vst1), fruits and vegetables (svfg), oil/fat (o1g), fish (fishg), tobacco smoking (smok) and alcohol drinking habit (alco). These were the main variables which showed statistical significance in the univariate analysis (results chapter) and none of these variables were highly correlated (table 4). In this way for each main exposure which was statistically significant in the univariate analysis, an adjusted ‘OR’, representing the odds of the exposure among cases to that among controls with 95% confidence limits was calculated to estimate the independent risk of getting prostate cancer when exposed to that factor. The adjusted odds ratios with 95% confidence limits for all other covariates which were not statistically significant in the univariate analysis and which were not highly correlated with the variables in the multivariate model were obtained by including these covariates one at a time in the original multivariate model. For those variables which were not statistically significant in the univariate model but correlated with any of the variables in the original multivariate model were obtained as described below:

Since fish (fishg) and meat (meatg) were highly correlated, the adjusted odds ratio for meat was obtained by replacing fish with meat in the original multivariate model. More precisely, the model for fish consisted of the variables: age (ageg), age at marriage (am1g), vasectomy (vst1), fruits and vegetables (svfg), oil/fat (o1g), fish (fishg), tobacco smoking (smok) and alcohol drinking habit (alco) and the model for meat consisted of the variables: age (ageg), age at marriage (am1g), vasectomy (vst1), fruits and vegetables (svfg), oil/fat (o1g), meat (meatg), tobacco smoking (smok) and alcohol drinking habit (alco).
The adjusted odds ratios for the different components of the main variables were obtained as described below:

The adjusted odds ratio for age at vasectomy (vst2g) (which is a component of the main exposure vasectomy (vst1)) was obtained by replacing vasectomy with age at vasectomy in the original multivariate model. More precisely, the model for age at vasectomy consisted of the variables: age (ageg), age at marriage (am1g), age at vasectomy (vst2g), fruits and vegetables (svfg), oil/fat (o1g), fish (fishg), tobacco smoking (smok) and alcohol drinking habit (alco) and the model for time since vasectomy (vst3g) consisted of the variables: age (ageg), age at marriage (am1g), time since vasectomy (vst3g), fruits and vegetables (svfg), oil/fat (o1g), fish (fishg), tobacco smoking (smok) and alcohol drinking habit (alco). The adjusted odds ratios for all the components of all other main exposures were obtained in a similar way.

The analysis was conducted using the Stata statistical software (version 7.0).
6. RESULTS

Risk estimation for all main exposures under study and at its various levels was carried out for the final 390 triplets which consisted of 390 cases and 780 controls.

6.1 Risk estimates: Unmatched analysis

6.1.1 Vasectomy and marital history

The distribution of the cases and controls by age-group, age at marriage, vasectomy status, age at vasectomy, and time since vasectomy and odds ratios with 95% CI in univariate and multivariate models are presented in table 5.

There was a significant difference of 6.8 years between the mean age of the cases and controls and so the controls were younger than the cases. This failure in age matching had occurred due to less number of old age men in the general population of Mumbai, India. So, some of the old cases were matched with young controls residing in the neighborhood of the cases. All the cases and controls were married and the mean age at marriage for the cases (21.2) was slightly higher than that of the controls (20.4). Age at marriage was categorized into three groups and it was found that higher proportion of the cases (16.4%) were married at the age of 25 years or later compared to that of the control group (5.0%). The risk estimates for age at marriage showed that there was a statistically significant 2.5 fold risk of getting prostate cancer for men who married at the age of 25 years or later compared to those who married before the age of 25 years (adjusted OR, table 5). Also there was a statistically significant increasing trend in risk was observed for an increase in the age at marriage (p for trend=0.01).

14.9% of the cases reported vasectomy compared to 10.0% of the controls. The risk of getting prostate cancer for men who reported having had vasectomy was 1.9 fold compared to those who did not and was statistically significant (adjusted OR, table 5).
Table 5. Distribution of cases and controls by age, marital history and vasectomy with odds ratios and 95% CI in univariate and adjusted models by unconditional logistic regression method.

<table>
<thead>
<tr>
<th>Background Characteristic</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>Univariate OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
<th>p trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>390 (100.0)</td>
<td>780 (100.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>16 (4.1)</td>
<td>58 (7.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–64</td>
<td>63 (16.2)</td>
<td>305 (39.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td>163 (41.8)</td>
<td>338 (43.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75–84</td>
<td>108 (27.7)</td>
<td>71 (9.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85+</td>
<td>40 (10.3)</td>
<td>8 (1.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>71.2</td>
<td>64.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at marriage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=19</td>
<td>82 (21.0)</td>
<td>200 (25.6)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>20–24</td>
<td>244 (62.6)</td>
<td>541 (69.4)</td>
<td>1.1 (0.8-1.5)</td>
<td>1.1 (0.8-1.5)</td>
<td></td>
</tr>
<tr>
<td>25+</td>
<td>64 (16.4)</td>
<td>39 (5.0)</td>
<td>4.0 (2.5-6.4)</td>
<td>2.5 (1.4-4.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean</td>
<td>21.2</td>
<td>20.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>332 (85.1)</td>
<td>702 (90.0)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58 (14.9)</td>
<td>78 (10.0)</td>
<td>1.6 (1.1-2.3)</td>
<td>1.9 (1.3-2.9)</td>
<td></td>
</tr>
<tr>
<td>Age at vasectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>25 (6.4)</td>
<td>33 (4.2)</td>
<td>1.6 (1.0-2.7)</td>
<td>2.1 (1.2-3.9)</td>
<td></td>
</tr>
<tr>
<td>45+</td>
<td>33 (8.5)</td>
<td>45 (5.8)</td>
<td>1.6 (1.0-2.5)</td>
<td>1.8 (1.1-2.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time since vasectomy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>22 (5.6)</td>
<td>65 (8.3)</td>
<td>0.7 (0.4-1.2)</td>
<td>1.2 (0.7-2.1)</td>
<td></td>
</tr>
<tr>
<td>25+</td>
<td>36 (9.2)</td>
<td>13 (1.7)</td>
<td>5.9 (3.1-11.2)</td>
<td>3.8 (1.9-7.6)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* the adjusted odds ratios were obtained by adjusting with age and all other covariates which showed statistical significance in the univariate analysis (age at marriage, vasectomy, fruits & vegetables, fish, oil/fat, tobacco smoking and alcohol drinking)

Age at vasectomy was grouped into two groups and it was observed that a higher proportion of cases (6.4%) had undergone vasectomy before the age of 45 years compared to that of the control group (4.2%). The risk for those who had a vasectomy before the age of 45 years was 2.1 fold and those who had it at a later age (at the age of 45 years or later) was 1.8 fold compared to those who did not had a vasectomy (adjusted OR, table 5). The linear trend for an increase in risk with a decrease in age at vasectomy was statistically significant (p for trend = 0.01).

A higher proportion of cases (9.2%) completed 25 years or more time since vasectomy compared to that of the control group (1.7%). The risk for those who completed
25 years or more time since vasectomy was 3.8 fold compared to those who did not had a vasectomy (adjusted OR, table 5). The linear trend for an increase in risk with an increase in time since vasectomy was highly significant (p for trend = 0.001).

6.1.2 Dietary habits

An attempt was made to study the role of certain dietary factors including vegetables and fruits, fish, meat, coffee, tea and oil/fat on the development of prostate cancer. The distribution of cases and controls by various dietary habits and odds ratios with 95% CI in univariate and adjusted models are presented in table 6.

58.7% of the control group consumed more than 3 kg of fruits and vegetables in a week compared to 52.1% of the case group. 31.7% of the control group consumed 2 to 3 kg of fruits and vegetables in a week compared to 26.4% of the case group Controlling for age and probable confounding factors, a statistically significant protective effect was observed for those who consumed fruits and vegetables 2 to 3 kg (OR 0.5, 95%CI 0.3-0.8) and more than 3 kg (OR 0.4, 95% CI 0.3-0.6) in a week compared to those who consumed less than 2 kg in a week. The linear trend in the protective effect was highly significant with an increase in the consumption of fruits and vegetables (p for trend = 0.001).

There was a slight variation between cases and controls with respect to consumption of fish and meat. Non fish consumers were higher in case group (39.5%) than that in the control group (31.8%). Non meat consumers were higher in the case group (27.9%) than in the control group (23.5%). The odds ratios for fish consumption did not show any significant protective effect even at higher quantities of fish consumption. Also the odds ratios for meat consumption did not show any significant risk even at higher quantities of meat consumption (adjusted OR, table 6) and there was no significant dose response (p for trends, table 6). Since fish and meat consumption were highly correlated and so two different models were prepared for fish and meat, so the odds ratio obtained for fish may also be attributable to meat and vise versa.

There was not any statistically significant risk or protective effect associated with coffee or tea consumption patterns of cases and controls ( adjusted OR, table 6) and not any significant dose response relationship (p for trend, table 6).

Even though not statistically significant, oil/fat consumption showed an elevated risk (OR 1.7) for those who consumed more than 2kg of oil/fat in a month compared to those who consumed less than 1kg oil/fat per month (adjusted OR, table 6).
Table 6. Distribution of cases and controls by various dietary habits with odds ratios and 95% CI in univariate and adjusted models by unconditional logistic regression method

<table>
<thead>
<tr>
<th>Background Characteristic</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>Univariate OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
<th>p trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>390 (100.0)</td>
<td>780 (100.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits and vegetables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(kg per week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>84 (21.5)</td>
<td>75 (9.6)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2–3</td>
<td>103 (26.4)</td>
<td>247 (31.7)</td>
<td>0.4 (0.3-0.5)</td>
<td>0.5 (0.3-0.8)</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>203 (52.1)</td>
<td>458 (58.7)</td>
<td>0.4 (0.3-0.6)</td>
<td>0.4 (0.3-0.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fish (kg per week)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>154 (39.5)</td>
<td>248 (31.8)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>100 (25.6)</td>
<td>239 (30.6)</td>
<td>0.7 (0.5-0.9)</td>
<td>1.1 (0.8-1.6)</td>
<td></td>
</tr>
<tr>
<td>Meat (kg per week)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>109 (27.9)</td>
<td>183 (23.5)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>119 (30.5)</td>
<td>274 (35.1)</td>
<td>0.7 (0.5-1.0)</td>
<td>1.2 (0.8-1.8)</td>
<td></td>
</tr>
<tr>
<td>Coffee (cups per week )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tea (cups per week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>26 (6.7)</td>
<td>32 (4.1)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>3–6</td>
<td>240 (61.5)</td>
<td>549 (70.4)</td>
<td>0.5 (0.3-0.9)</td>
<td>0.9 (0.5-1.7)</td>
<td></td>
</tr>
<tr>
<td>7+</td>
<td>124 (31.8)</td>
<td>199 (25.5)</td>
<td>0.8 (0.4-1.3)</td>
<td>1.1 (0.6-2.2)</td>
<td>0.15</td>
</tr>
<tr>
<td>Oil/Fat (kg per month)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>69 (17.7)</td>
<td>138 (17.7)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>291 (74.6)</td>
<td>617 (79.1)</td>
<td>0.9 (0.7-1.3)</td>
<td>0.9 (0.6-1.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>30 (7.7)</td>
<td>25 (3.2)</td>
<td>2.4 (1.3-4.4)</td>
<td>1.7 (0.9-3.3)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

* the adjusted odds ratios were obtained by adjusting with age and all other covariates which showed statistical significance in the univariate analysis (age at marriage, vasectomy, fruits & vegetables, fish, oil/fat, tobacco smoking and alcohol drinking)

6.1.3 Tobacco habits

Tobacco for smoking is available in two forms, bidi and cigarette. Bidi is stronger than cigarette in terms of nicotine contents. It can be observed from table 7 that the habit of tobacco smoking and tobacco chewing were slightly higher in the control group than in the case group. Overall tobacco smoking, either bidi or cigarette smoking, were 75.9% in the case group and 81.0% in the control group. Only 9.0% of the cases were bidi smokers compared to 9.5% of the controls. 67.4% of the cases were cigarette smokers compared to 71.7% of the controls. Among tobacco chewers, 13.1% were cases and 14.2% were controls.
Table 7. Distribution of cases and controls by various tobacco habits with odds ratios and 95% CI in univariate and adjusted models by unconditional logistic regression method.

<table>
<thead>
<tr>
<th>Background Characteristic</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>Univariate OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
<th>p</th>
<th>trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>390 (100.0)</td>
<td>780 (100.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>94 (24.1)</td>
<td>148 (19.0)</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Yes</td>
<td>296 (75.9)</td>
<td>632 (81.0)</td>
<td>0.7 (0.6-0.9)</td>
<td>1.2 (0.8-1.7)</td>
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<tr>
<td>Bidi smoking</td>
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</tr>
<tr>
<td>No</td>
<td>355 (91.0)</td>
<td>706 (90.5)</td>
<td>1.0</td>
<td>1.0</td>
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<td>Yes</td>
<td>35 (9.0)</td>
<td>74 (9.5)</td>
<td>0.9 (0.6-1.4)</td>
<td>0.9 (0.6-1.4)</td>
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<tr>
<td>Number smoked per day</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>1–5</td>
<td>11 (2.8)</td>
<td>37 (4.7)</td>
<td>0.6 (0.3-1.2)</td>
<td>0.6 (0.3-1.2)</td>
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</tr>
<tr>
<td>6–10</td>
<td>9 (2.3)</td>
<td>26 (3.3)</td>
<td>0.7 (0.3-1.4)</td>
<td>0.6 (0.3-1.5)</td>
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</tr>
<tr>
<td>11+</td>
<td>15 (3.8)</td>
<td>10 (1.3)</td>
<td>2.9 (1.3-6.7)</td>
<td>2.7 (1.1-6.7)</td>
<td>0.35</td>
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</tr>
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<td>Time since start of habit</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>5 (1.3)</td>
<td>20 (2.6)</td>
<td>0.5 (0.2-1.3)</td>
<td>1.0 (0.4-2.8)</td>
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<tr>
<td>30–49</td>
<td>18 (4.6)</td>
<td>43 (5.5)</td>
<td>0.8 (0.5-1.5)</td>
<td>0.8 (0.4-1.5)</td>
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<tr>
<td>50+</td>
<td>12 (3.1)</td>
<td>11 (1.4)</td>
<td>2.2 (0.9-5.0)</td>
<td>1.1 (0.4-2.7)</td>
<td>0.68</td>
<td></td>
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<tr>
<td>Cigarette smoking</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>127 (32.6)</td>
<td>221 (28.3)</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Yes</td>
<td>263 (67.4)</td>
<td>559 (71.7)</td>
<td>0.8 (0.6-1.1)</td>
<td>1.2 (0.9-1.7)</td>
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</tr>
<tr>
<td>Number smoked per day</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>135 (34.6)</td>
<td>328 (42.1)</td>
<td>0.7 (0.5-1.0)</td>
<td>1.1 (0.7-1.5)</td>
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<td>6–10</td>
<td>107 (27.4)</td>
<td>209 (26.8)</td>
<td>0.9 (0.7-1.2)</td>
<td>1.5 (0.9-2.2)</td>
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<td>11+</td>
<td>23 (5.9)</td>
<td>22 (2.8)</td>
<td>1.8 (0.9-3.3)</td>
<td>1.5 (0.7-3.2)</td>
<td>0.09</td>
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<tr>
<td>Time since start of habit</td>
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</tr>
<tr>
<td>&lt;30</td>
<td>51 (13.1)</td>
<td>223 (28.6)</td>
<td>0.4 (0.3-0.6)</td>
<td>1.1 (0.7-1.7)</td>
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<tr>
<td>30–49</td>
<td>145 (37.2)</td>
<td>290 (37.2)</td>
<td>0.9 (0.6-1.2)</td>
<td>1.3 (0.9-1.9)</td>
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<tr>
<td>50+</td>
<td>67 (17.2)</td>
<td>46 (5.9)</td>
<td>2.5 (1.6-3.9)</td>
<td>1.3 (0.7-2.2)</td>
<td>0.16</td>
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</tr>
<tr>
<td>Tobacco chewing</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>339 (86.9)</td>
<td>669 (85.8)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51 (13.1)</td>
<td>111 (14.2)</td>
<td>0.9 (0.6-1.3)</td>
<td>0.8 (0.5-1.2)</td>
<td></td>
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</tr>
<tr>
<td>Number chewed per day</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1–5</td>
<td>38 (9.7)</td>
<td>85 (10.9)</td>
<td>0.9 (0.6-1.3)</td>
<td>0.8 (0.5-1.2)</td>
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<td></td>
</tr>
<tr>
<td>6–10</td>
<td>10 (2.6)</td>
<td>20 (2.6)</td>
<td>1.0 (0.5-2.1)</td>
<td>0.7 (0.3-1.7)</td>
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<td></td>
</tr>
<tr>
<td>11+</td>
<td>3 (0.8)</td>
<td>6 (0.8)</td>
<td>1.0 (0.3-4.0)</td>
<td>0.9 (0.2-4.3)</td>
<td>0.24</td>
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<tr>
<td>Time since start of habit</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>7 (1.8)</td>
<td>59 (7.6)</td>
<td>0.3 (0.1-0.6)</td>
<td>0.3 (0.1-0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–49</td>
<td>26 (6.7)</td>
<td>37 (4.7)</td>
<td>1.4 (0.8-2.3)</td>
<td>1.1 (0.6-2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>18 (4.6)</td>
<td>15 (1.9)</td>
<td>2.4 (1.2-4.8)</td>
<td>1.0 (0.4-2.2)</td>
<td>0.67</td>
<td></td>
</tr>
</tbody>
</table>

* the adjusted odds ratios were obtained by adjusting with age and all other covariates which showed statistical significance in the univariate analysis (age at marriage, vasectomy, fruits & vegetables, fish, oil/fat, tobacco smoking and alcohol drinking)
Overall tobacco smoking did not show any statistically significant association with prostate cancer (adjusted OR, table 7). Since most of the tobacco smokers were cigarette smokers, the odds ratio obtained for tobacco smoking may also be attributable to cigarette smoking. The overall tobacco smokers were categorized into bidi and cigarette smokers and the risk at different levels were estimated in these two groups.

Neither bidi smoking nor cigarette smoking showed any statistically consistent association with prostate cancer, when compared with no bidi or no cigarette smokers (adjusted ORs, table 7). Number of bidies or cigarettes smoked per day and time since start of these habits did not show any consistent dose-response association (p for trend, table 7).

Tobacco is used in another form as chew-mix. After chewing the tobacco mix, part of the water coming out from the chew-mix will be swallowed and part will be taken out along with the chew-mix. This is a common habit among a minority group. The risk among tobacco chewers showed no statistically significant association with prostate cancer (adjusted OR, table 7) and there was no dose response for number of times chewed per day or time since start of the habit (p for trend, table 7).

The adjusted odds ratios were slightly lower for bidi smoking and tobacco chewing habits but slightly higher for cigarette smoking when compared with the univariate odds ratios (table 7).

### 6.1.4 Alcohol habits

Alcoholic beverages available in Mumbai are of two types: ‘foreign beverages’ (processed drinks such as wine, whisky, beer, etc.) and ‘local beverages’ (non processed drinks used locally such as toddy, arrack, etc.). The main foreign beverages drank by cases and controls were wine and whisky, and toddy was the main local beverage drank by cases and controls. Very few cases and controls reported the habit of beer drinking and so these cases and controls were included with wine drinkers and so wine drinkers include few beer drinkers also. Similarly very few cases and controls reported the habit of arrack drinking and these cases and controls were included with toddy drinkers and so toddy drinkers include few arrack drinkers also.
It was observed that among foreign beverage drinkers (wine and whisky), the proportion of cases were slightly lower than that of the controls, 19.5% of the cases were wine drinkers compared to 22.8% of the controls and 52.1% of the cases were whisky drinkers compared to 63.2% of the controls. Among local beverage drinkers (toddy), the proportion of cases (6.7%) were slightly higher than the controls (5.8%) (table 8).

Overall alcohol drinking habits showed a decreased risk in univariate but disappeared in the multivariate model and showed no statistically significant association for prostate cancer compared with non drinkers (adjusted OR, table 8). Since most of the alcohol drinkers were whisky drinkers, the odds ratio obtained for alcohol drinking may also be attributable to whisky drinking.

Wine drinking showed no statistically significant increased or decreased risk for prostate cancer (adjusted OR, table 8), also number of times wine drank per week and time since start of the wine drinking habit showed no dose response (p for trend, table 8).

Whisky drinking showed a decreased risk in univariate but the decreased risk was not statistically significant after adjusting (adjusted OR, table 8), also number of times whisky drank per week or time since start of the habit showed no statistically significant dose response (p for trend, table 8).

A slightly increased risk seen for toddy drinking habit was not statistically significant after adjustment (adjusted OR, table 8). Number of times toddy drank per week or time since start of toddy drinking habit showed no dose response relationship (p for trend, table 8).

The adjusted odds ratios were slightly higher than the crude odds ratios for wine and whisky but were slightly lower for toddy drinking habits (table 8).
Table 8: Distribution of cases and controls by various alcohol habits with odds ratios and 95% CI in univariate and adjusted models by unconditional logistic regression method

<table>
<thead>
<tr>
<th>Background Characteristic</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>Univariate OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
<th>p trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>390 (100.0)</td>
<td>780 (100.0)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>113 (29.0)</td>
<td>111 (14.2)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>277 (71.0)</td>
<td>669 (85.8)</td>
<td>0.4 (0.3-0.7)</td>
<td>0.6 (0.4-1.1)</td>
<td></td>
</tr>
<tr>
<td>Wine drinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>314 (80.5)</td>
<td>602 (77.2)</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>76 (19.5)</td>
<td>178 (22.8)</td>
<td>0.8 (0.6-1.1)</td>
<td>1.0 (0.7-1.4)</td>
<td></td>
</tr>
<tr>
<td>No. of times drank per week</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One time or less</td>
<td>34 (8.7)</td>
<td>91 (11.7)</td>
<td>0.7 (0.5-1.1)</td>
<td>0.8 (0.5-1.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>More than one time</td>
<td>42 (10.8)</td>
<td>87 (11.2)</td>
<td>0.9 (0.6-1.4)</td>
<td>1.2 (0.8-1.8)</td>
<td>0.68</td>
</tr>
<tr>
<td>Time since start of habit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>33 (8.5)</td>
<td>99 (12.7)</td>
<td>0.6 (0.4-1.0)</td>
<td>0.9 (0.6-1.5)</td>
<td>0.89</td>
</tr>
<tr>
<td>25+</td>
<td>43 (11.0)</td>
<td>79 (10.1)</td>
<td>1.0 (0.7-1.6)</td>
<td>1.1 (0.7-1.6)</td>
<td>0.89</td>
</tr>
<tr>
<td>Whisky drinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>187 (47.9)</td>
<td>287 (36.8)</td>
<td>1.0</td>
<td>1.0</td>
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</tr>
<tr>
<td>Yes</td>
<td>203 (52.1)</td>
<td>493 (63.2)</td>
<td>0.6 (0.5-0.8)</td>
<td>0.6 (0.5-1.1)</td>
<td></td>
</tr>
<tr>
<td>No. of times drank per week</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One time or less</td>
<td>149 (38.2)</td>
<td>410 (52.6)</td>
<td>0.6 (0.4-0.7)</td>
<td>0.6 (0.5-1.0)</td>
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<tr>
<td>More than one time</td>
<td>54 (13.8)</td>
<td>83 (10.6)</td>
<td>1.0 (0.7-1.2)</td>
<td>0.8 (0.5-1.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Time since start of habit</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>82 (21.0)</td>
<td>232 (29.7)</td>
<td>0.5 (0.4-0.7)</td>
<td>0.7 (0.5-1.1)</td>
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<tr>
<td>25+</td>
<td>121 (31.0)</td>
<td>261 (33.5)</td>
<td>0.7 (0.5-0.9)</td>
<td>0.7 (0.5-1.0)</td>
<td>0.11</td>
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<td>Toddy drinking</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>364 (93.3)</td>
<td>735 (94.2)</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Yes</td>
<td>26 (6.7)</td>
<td>45 (5.8)</td>
<td>1.2 (0.7-1.9)</td>
<td>1.0 (0.6-1.8)</td>
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<tr>
<td>No. of times drank per week</td>
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<td></td>
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</tr>
<tr>
<td>One time or less</td>
<td>24 (6.2)</td>
<td>37 (4.7)</td>
<td>1.3 (0.8-2.2)</td>
<td>1.2 (0.6-2.1)</td>
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</tr>
<tr>
<td>More than one time</td>
<td>2 (0.5)</td>
<td>8 (1.0)</td>
<td>0.5 (0.1-2.4)</td>
<td>0.5 (0.1-2.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>Time since start of habit</td>
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<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>16 (4.1)</td>
<td>29 (3.7)</td>
<td>1.1 (0.6-2.1)</td>
<td>1.1 (0.6-2.2)</td>
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<tr>
<td>25+</td>
<td>10 (2.6)</td>
<td>16 (2.1)</td>
<td>1.3 (0.6-2.8)</td>
<td>0.9 (0.4-2.1)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

* the adjusted odds ratios were obtained by adjusting with age and all other covariates which showed statistical significance in the univariate analysis (age at marriage, vasectomy, fruits & vegetables, fish, oil/fat, tobacco smoking and alcohol drinking)
6.2 Risk estimates: Matched analysis

Even though this study was conducted as a matched case control study (matched for age and place of residence), as mentioned earlier due to failure in age matching, unmatched logistic regression analysis was carried out for risk estimates.

For the purpose of comparing the variation in the risk estimates by unmatched and matched analysis, conditional logistic regression analysis was carried out for those covariates which remain significant after adjustment in the logistic regression (unmatched) model. In the multivariate model (unmatched), the exposures, age at marriage, vasectomy, age at vasectomy, time since vasectomy, and fruits and vegetables remain significant after adjustment.

Table 9. Adjusted odds ratios with 95% CI for marital history, vasectomy and intake of fruits and vegetables by unconditional and conditional logistic regression method

<table>
<thead>
<tr>
<th>Background Characteristic</th>
<th>Cases(%)</th>
<th>Controls (%)</th>
<th>Unconditional</th>
<th>Conditional</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adjusted*</td>
<td>Adjusted*</td>
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<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>p trend</td>
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<td>Age at marriage</td>
<td></td>
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<tr>
<td>&lt;=19</td>
<td>82 (21.0)</td>
<td>200 (25.6)</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>20–24</td>
<td>244 (62.6)</td>
<td>541 (69.4)</td>
<td>1.1 (0.8-1.5)</td>
<td>1.2 (0.7-2.0)</td>
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<td>25+</td>
<td>64 (16.4)</td>
<td>39 (5.0)</td>
<td>2.5 (1.4-4.3)</td>
<td>0.01</td>
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<td>Vasectomy</td>
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<tr>
<td>No</td>
<td>332 (85.1)</td>
<td>702 (90.0)</td>
<td>1.0</td>
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</tr>
<tr>
<td>Yes</td>
<td>58 (14.9)</td>
<td>78 (10.0)</td>
<td>1.9 (1.3-2.9)</td>
<td>1.6 (0.9-2.9)</td>
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<td>Age at vasectomy</td>
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<tr>
<td>&lt;45</td>
<td>25 (6.4)</td>
<td>33 (4.2)</td>
<td>2.1 (1.2-3.9)</td>
<td>2.0 (0.9-4.4)</td>
</tr>
<tr>
<td>45+</td>
<td>33 (8.5)</td>
<td>45 (5.8)</td>
<td>1.8 (1.1-2.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time since vasectomy</td>
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<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>22 (5.6)</td>
<td>65 (8.3)</td>
<td>1.2 (0.7-2.1)</td>
<td>1.0 (0.4-2.1)</td>
</tr>
<tr>
<td>25+</td>
<td>36 (9.2)</td>
<td>13 (1.7)</td>
<td>3.8 (1.9-7.6)</td>
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<td>Fruits and vegetables</td>
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<tr>
<td>(kg per week)</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 1</td>
<td>84 (21.5)</td>
<td>75 (9.6)</td>
<td>1.0</td>
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<td>1-3</td>
<td>103 (26.4)</td>
<td>247 (31.7)</td>
<td>0.5 (0.3-0.8)</td>
<td>0.3 (0.1-0.6)</td>
</tr>
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<td>&gt;3</td>
<td>203 (52.1)</td>
<td>458 (58.7)</td>
<td>0.4 (0.3-0.6)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* the adjusted odds ratios were obtained by adjusting with age and all other covariates which showed statistical significance in the univariate analysis (age at marriage, vasectomy, fruits & vegetables, fish, oil/fat, tobacco smoking and alcohol drinking)
It can be seen from table 9 that there are not much variation in the risk estimates by both methods (unconditional and conditional) except for age at marriage. As regarding the variation in the risk estimates with an increase in the age at marriage, the unconditional analysis results showed a gradually increasing trend, where as the matched analysis results showed a sudden increase in the risk estimate for those who married at the age of 25 years or later. This is probably because in conditional analysis only discordant pairs in outcomes are considered whereas all the observations are used in the logistic regression (unconditional). The same reason explains for the insignificant odds ratios for vasectomy and age at vasectomy in the matched analysis, which were significant when estimated by unmatched analysis. Power of the study will be increased when performing an unmatched analysis of the matched data. However, unmatched analysis is performed for the matched data only if the matched sets did not meet the criteria of matching.
7. DISCUSSION

7.1 Study Base

In this study we included only microscopically proved incident cases of prostate cancer registered in the geographical area covered by the Bombay Population Based Cancer Registry so that misclassification of cases is unlikely. The area covered by this registry is one of the districts of Maharashtra state having 100% urban population. The data collected by the Bombay Cancer Registry has been shown both complete and reliable (Yeole and Jussawalla 1998, Yeole 2001, NCRP 2000). So the study base is expected to be of acceptable standard.

As mentioned earlier in the thesis, in the demographic profile of India, that is, ‘since independence, the Indian government has emphasized family planning through contraceptive use. In 2000, estimates indicated that 48% of (married) Indian women were using a method of contraception; 43% used a method of modern contraception. Among couples, who used any method of contraception, 67% of all use was female sterilization and 10% was male sterilization’. The prevalence of the main exposure under study, vasectomy, among controls (10.0%) was comparable to the prevalence of vasectomy in the general population of India (10.0%). So the controls might be representative of the general population for the exposure of vasectomy even though there are several limitations.

India is the second largest producer and forth largest exporter of tobacco in the world (Sundaram 2003). It is estimated that in India, 65% of all men and 33% of all women use some form of tobacco (Shimkhada et al. 2003). Also there are wide variations in the consumption pattern of urban and rural household as well as various socio-economic classes in India. It is interesting to note that smokeless tobacco is more prevalent among low income class and scheduled tribes, where as, smoking is more prevalent among middle and high-income class as well as in the general community (Rijo 2003). These figures were approximately consistent with the smoking prevalence in the study population taking into account the variations in the consumption pattern of urban, rural and various socio-economic classes. We assume that the exposure history collected from cases and controls
for all other variables in this study might be reliable and are of acceptable standard even though there are several limitations.

Since the case control group consisted of male population, and a male social investigator was recruited, the reliability of the information on certain exposures such as vasectomy, tobacco and alcohol habits and certain dietary habits were probably improved. Some study subjects might have considered the questions on vasectomy sensitive; such men might have felt more comfortable providing accurate information to male interviewers. A good effort was made in the present study to collect reliable information by establishing good rapport with the subjects and also by using certain surrogate variables in the interviews and information has been collected from the cases and controls by face to face personal interviews.

Certain weaknesses should be taken into consideration while interpreting the results from this study. There are various kinds of problems in eliciting information from cases and controls, especially on family planning, tobacco and alcohol habits, and various kinds of dietary consumption habits, etc., because of the socio-cultural implications in the Indian society. This was overcome to some extent by obtaining other details such as age at marriage, whether he was smoking/chewing/drinking before or started later, the common units in which he purchased bidis, cigarettes, how much money he spent on them etc. Moreover, although the objective or hypothesis of the study was not made known to the interviewer, blinding could not be ensured in the present study. The controls were disease free and younger than the cases, so there might be chances for an information bias on the reporting of the previous exposure history for certain exposures by cases and controls.

Besides the usual problem of dependence on recall, which is common to all case control studies, the collection of data on some exposure parameters posed the additional problem of measuring the usual intake/exposure levels prior to disease onset in meaningful quantitative terms. Nevertheless, this kind of non-differential misclassification can happen to both the case and control group, at the comparison stage this bias will be minimized.

Although efforts were made to interview all the 594 microscopically proved cases to be included for this study, only 390 cases (65.7%) were available to be included for final analysis and 204 cases (34.3%) were dropped due to migration, door closed, not willing to give personal details, too old/died and proxy respondents were not available or not cooperative to complete the interview, no eligible controls were available in the neighborhoods, controls were not willing to give personal details etc. So there may be a possibility for selection bias. Any differences in the exposure history between the cases included and dropped may result in biased and inconsistent estimates. Yet, in control
selection, since we have used population based controls, the bias in the selection of controls might have minimised. The prevalence of the main exposure under study, vasectomy, among controls (10.0%) was comparable to the prevalence of vasectomy in the general population of India (10.0%).

For many of the cases, it was not possible to find the proper age matched controls residing in the neighborhood of the respective cases due to less number of old age men in the general population of Mumbai and especially in the neighborhood of the respective cases. More than 60% of the age matched case-control triplets included in the study for final analysis have had an age difference of more than +5 years between the case-control pairs or triplets and hence a failure in age matching occurred. Controls were significantly younger than the cases. This can induce various types of biases in the study and in the reporting of the exposure history between cases and controls.

156 (40.0%) cases among the 390 cases included in the final analysis were died/ were in very serious conditions before conducting an interview and the information for these 156 cases were collected by proxy respondents. For the remaining 234 (60.0%) cases, information is reported by self. For all the 780 controls included in the final analysis, information is assumed to be reported by self. The reliability, accuracy and completeness of the information reported by proxies may vary from those reported by self. Also the nature, degree, or direction of recall bias among proxies reporting will also vary and this may result in biased and inconsistent estimates.

There were deficiencies in filling of the questionnaire especially for some components of tobacco and alcohol habits. The unusual correlation among different alcohol habits (such as a negative correlation among whisky drinkers and wine drinkers) were also suggestive of deficiencies in abstracting this information. In the questionnaire, for some components of alcohol and tobacco, only known habits were being filled and all the remaining being kept blank. It was impossible to separate out ‘no habits’ and ‘unknown habits’ from these blanks and in the analysis, all these blanks were interpreted as ‘no habits’. However, this was probably not selective for cases and controls.

The habits, customs, and life style of people are very complex and vary from person to person. It is difficult to ascertain whether the estimates obtained for one factor is an absolute estimate or confounded by many other unmeasured factors or highly correlated factors directly or indirectly. A look on the correlation of the factors under study revealed that all factors are correlated at varying levels and when there is a high correlation between two factors, it is difficult to assess whether the estimates obtained are due to the one or the other and we can only assess that it may be due to either of the two.
7.2 Comparison of the results with other studies

7.2.1 Vasectomy

There has been concern over a positive association between vasectomy and prostate cancer since the late 1980’s when Honda et al. (1988) first reported findings from their population based case control study. This relation remains controversial with some studies reporting a positive (Mettlin et al. 1990, Rosenberg et al. 1990, Spitz et al. 1991, Hayes et al. 1993, Giovannucci et al. 1993b, Giovannucci et al. 1993c, Hsing et al. 1994, Lesko et al 1996) and others no association (Rosenberg et al. 1994, John et al. 1995, Sidney et al. 1991, Zhu et al. 1996, Strayer 2002, Lyng 2002, Cox et al. 2002). Several other studies have reported an association between vasectomy and prostate cancer, with RR’s as high as 6.7 in 1 case control study and 1.9 in some cohort studies (Mettlin et al. 1990, Rosenberg et al. 1990, Giovannucci et al. 1993b, Giovannucci et al. 1993c, Hsing et al. 1994). In a recent meta-analysis (Dennis et al. 2002) examining vasectomy status, age at vasectomy, and time since vasectomy the pooled relative risk estimate for those who had had a vasectomy compared with those who did not was 1.37 (95% CI 1.15-1.62) based on five cohort studies and 17 case-control studies. The relative risk estimate varied by study design with the lowest risk for population based case control studies. In a case control study conducted in China, the RR varied from 2.0 to 6.7, depending on the control series used in the analysis, indicating the degree to which selection bias may influence the results (Hsing et al. 1994). A systematic review of the literature was published by Bernal-Delgado et al. (1998), which documented the lack of a significant relationship between vasectomy and prostate cancer. Only 3 of the 14 studies determined vasectomy status by methods other than self-report (Bernal-Delgado et al. 1998). None of these reported an association and this shows the bias about the collection of information. Interestingly, 11 of the 14 studies evaluated in this review reported the existence of an excess risk. In 6 of these studies, the association was statistically significant but Bernal-Delgado et al. (1998) demonstrated the existence of numerous methodological problems especially in the studies that showed the greatest increase in risk. A review of the literature by DerSimonian et al. (1993) also found the evidence to be conflicting with several methodological errors.
A number of mechanisms have been proposed to explain how vasectomy may increase the risk of prostate cancer (Howards 1993). A report of John et al states that the ratio of dihydrotestosterone-to-testosterone was higher and the serum concentration of sex hormone binding globulin was lower in men who underwent vasectomy versus those who did not (John et al. 1995), most previous studies have failed to determine a relationship between vasectomy and circulating androgens (Richards et al. 1981).

The present study suggested that vasectomy is a risk factor for prostate cancer. The risk was higher in those who had it at an earlier age and the risk increased as the time since vasectomy increased. There was a significant trend of increasing risk with increasing time since vasectomy and also with an earlier age at vasectomy. These findings were consistent with many of the earlier studies (Honda et al. 1988, Mettlin et al. 1990, Rosenberg et al. 1990, Spitz et al. 1991, Hayes et al. 1993, Giovannucci et al. 1993b, Giovannucci et al. 1993c, Hsing et al. 1994) and also with the earlier pilot hospital based case control study conducted in India (Platz et al. 1997). In the pilot study the risk of prostate cancer associated with vasectomy appeared to be higher among men who underwent vasectomy at least two decades prior to cancer diagnosis or who were at least 40 years old at vasectomy (Platz et al. 1997).

Two main criticisms of those studies purporting a positive association are that detection bias or confounding might have produced a spurious association between vasectomy and prostate cancer (Chacko et al. 2002). For example, detection bias might have arisen if those who underwent vasectomy were more likely to have repeated medical contact with greater opportunity for screening, and thus, detection of asymptomatic prostate cancer. In our study detection bias is unlikely. Cases and controls were drawn from a population in India where screening for prostate cancer was not customary and most cases were symptomatic at diagnosis. Confounding might have gone unnoticed because the majority of the positive studies published to date have been conducted in the US where those dietary and lifestyle factors that potentially confound the relation between vasectomy and prostate cancer may be operating similarly in each study. We controlled for confounding in our analysis by including age, marital history, tobacco and alcohol habits, dietary habits, etc. Residual confounding by these factors cannot be entirely ruled out, however.

Since 204 cases (34.3%) among the 594 eligible cases were dropped due to several reasons as mentioned earlier, there may be a possibility for selection bias. Any differences in the exposure history between the cases included and dropped may result in biased and inconsistent estimates. Yet, for the controls, since we have used population based controls,
the bias in the selection of controls might have minimised. The prevalence of vasectomy among controls (10.0%) were comparable to the prevalence of vasectomy in the general population of India (10.0%).

However, several limitations should be considered for the estimated high risk of prostate cancer in vasectomized men. It may be due to any unmeasured confounding because the etiology of prostate cancer is largely unknown. It is impossible, therefore, to assure that true risk factors for prostate cancer are equally distributed between men who had undergone vasectomy and men who had not. The Nurses’ Health Study (Giovannucci et al. 1992) indicated that men who underwent vasectomy had a lower total mortality than men who did not. Men who underwent vasectomy in that study must, therefore, have different characteristics from men who did not. It is entirely possible that some of these characteristics increases the risk of prostate cancer. Regarding confounding factors, it of course remains true that we know little about the actual etiology of prostate cancer.

Potential information bias from proxy respondents is a concern in this study. The results from additional analysis restricted to direct respondents yielded an adjusted but insignificant (the statistical insignificance can be due to the decrease in sample size) odds ratio of 1.4, indicating a substantial reduction in risk for vasectomy compared with the results for vasectomy (OR 1.9, 95% CI 1.3-2.9) from including proxy respondents.

Reporting bias may account for the difference in estimates of risk based on information by self reporting and by a proxy. It is important to note that for 40% of the cases who were dead or in advanced conditions, the information was reported by proxies and since vasectomy is a sort of operation and the cases were seriously hospitalised, the proxies might have tended to answer positive for vasectomy. This might have caused over reporting of vasectomy for cases. The controls were all younger and healthy persons and because vasectomy was self reported, there is possibility for selective under reporting since vasectomy is a very personal and in fact humiliating a man’s personality to express in front of family members and relatives. The dose response relationship on age at vasectomy and time since vasectomy may also be due to some psychosocial background, the crudest family planning policy occurred in the youth of these men. It may also have been especially embarrassing to have vasectomy at a young age. In summary, it is likely that the reported estimate of prevalence of vasectomy in cases were over reported and that in controls were under reported. Both biases tend to result in high estimates of odds ratio.

The impact of any reduction in popularity of vasectomy attributable to concerns regarding prostate cancer is most likely to be felt in developing countries, particularly in several countries in Asia and Africa where maternal and infant mortality rates are high and
vasectomy programs are just beginning to grow. If vasectomy is a risk factor for prostate cancer, people need to know and informed choices need to be made. By contrast, if associations are spurious but believed to be real, the popularity of a highly effective contraceptive will be reduced, opportunities to reduce unintended pregnancy will be lost, and maternal and infant mortality and morbidity will increase. Due to the several limitations and possibilities for reporting biases in this study, the evidence for the estimates of the higher odds ratio for prostate cancer in vasectomised men may not be a strong one. Because of the importance of vasectomy for fertility control, further studies with good design and conduct (the information on vasectomy need to be collected with better reliability) are required to clarify the issue of vasectomy associations with prostate cancer.

7.2.2 Marital history

Very few studies were conducted around the world to assess the association of marital history and prostate cancer. In the present study all men were married, and so only age at marriage was studied as a measure of marital history. The present study indicated that late marriage, that is, men who married after the age of 25 years, was associated with a 2.5 fold risk for prostate cancer compared with those who married at younger ages, before the age of 25 years, a finding consistent with some of the earlier studies. In an earlier case control study conducted in Italy (La Vecchia et al. 1993) and another case control study conducted in Athens, Greece, which reported a suggestion that sexual activity in early adulthood may be inversely associated with prostate cancer risk (Hsieh et al. 1999). A recent meta analysis (Dennis and Dawson 2002) reported an increased risk of prostate cancer with greater sexual activity (OR1.2, 95% CI 1.1-1.3 for an increase in sexual activity of 3 times per week). But these findings are questionable because of problems with study design. In many of the studies, the data were collected by asking elderly men with and without prostate cancer about sexual events that occurred decades in the past. Men who have been diagnosed with a disease, such as prostate cancer, that can affect their sexual functioning, may recall past sexual events differently than healthy men do. Prospective data on self-reported sexual activity and prostate cancer are restricted to 2 investigations. These studies (Mills et al. 1989, Severson et al. 1989) considered age at first marriage, marital status, and number of children as measures of sexual activity and found no association between these factors and prostate cancer. A few other studies reported no association of marital history or age at marriage and prostate cancer (Dennis and Dawson 2002, Ewertz et al. 2001, Ilic et al.
Another study reported a reverse association of age at first marriage (early high, late low) and prostate cancer (Merrill et al. 2002).

Sexual activity is hypothesized to affect prostate carcinogenesis through numerous etiologic pathways. One of the most commonly postulated mechanisms implicates increased sexual activity as an indicator of higher androgenic activity and thus a marker for a high-risk population (Krain 1974). Another mechanism proposes that sexual activity represents a marker for opportunity for exposure to infectious agents, although no sexually transmitted infection has been consistently implicated in prostate cancer development (Strickler and Goedert 2001). In a very recent study, the risk of prostate cancer was increased among men with a history of venereal disease (odds ratio = 1.7, 95% CI = 1.1-2.5). A higher frequency of cases reported having had sex with prostitutes. A significant increased risk was observed in subjects who reported having sexual intercourse more than 7 times per week compared with those who reported a weekly frequency of 3 times or fewer (OR 2.1, 95% CI 1.2-3.7). Moreover, a significant trend was demonstrated. The study supports the hypothesis that an infectious factor related to sexual behavior could be involved in the occurrence of prostate cancer (Fernandes et al. 2005). An alternative hypothesis suggests that a reduced ejaculatory output in otherwise normal men is an etiologic risk factor for prostate cancer. That proposition is based on the theory that infrequent ejaculation increases the risk of prostate cancer because of retained carcinogenic secretions in the prostatic acini (Isaacs 1983). A further hypothesis implicates repression of sexuality as a risk factor for prostate cancer and is derived from reports of greater sexual drive coupled with deprived sexual activity (Rotkin 1977) and greater interest in more sexual intercourse than experienced (Steele et al. 1971) among prostate cancer cases compared with controls. In the United States, 38% of married persons aged 60 years or older reportedly engage in sexual activity between 1 and 4 times per month, and 14% indicate being sexually active at least 5 times per month (Marsiglio and Donnelly 1991). Although the libido declines with age, sexual activity is common among 70-, 80-, and even 90-year-old men (Bortz et al. 1999). Given that sexual activity is common, including in older men, (Marsiglio and Donnelly 1991, Bortz et al. 1999) and that prostate cancer risk is high, (Jemal et al. 2003) any association between these factors would have clinical and public health relevance. Epidemiological data on sexual activity and prostate cancer are almost entirely limited to case-control studies, which may be particularly prone to methodological bias because information on prediagnosis sexual activity is collected after the diagnosis of cancer. Sexual function may diminish after the diagnosis of prostate cancer and its treatment, (Jakobsson et al. 2001) and recall of past levels of sexual activity among
individuals with prostate cancer could be distorted as a consequence of prostate malignancy or ongoing therapy. The differences in recall could distort the results of a study. Although these results do not show a totally cohesive picture, they suggest that some aspects of sexual lifestyle may be associated with prostate cancer. Overall, the association of marital history and prostate cancer is not consistent.

7.2.3 Dietary habits

The role of diet in the etiology of prostate cancer remains unclear. Many researchers have observed that it is not easy to quantify the contribution of diet to cancer risk. It is very difficult to separate the effect of a given nutrient from other parts of the diet and to identify an association with a given cancer (Kaul et al. 1987, Severson et al. 1989). Nonetheless, this study provided some clues for further investigation into the role of diet in prostate cancer.

7.2.3.1 Fruits and vegetables

Increased dietary intake of fruits and vegetables has been associated with a reduced risk of prostate cancer in some studies. In the present study, consumption of more quantities of fruits and vegetables (2 to 3 kilograms or more than 3 kilogram per week) showed a protective effect for prostate cancer compared with those who consumed less than 2 kilograms of fruits and vegetables per week, consistent with many of the earlier studies. In a recent case-control study conducted in Hangzhou, southeast China during 2001–2002, the prostate cancer risk was declined with increasing consumption of lycopene, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein and zeaxanthin, and intake of tomatoes, pumpkin, spinach, watermelon and citrus fruits were also inversely associated with the prostate cancer risk (Jian et al. 2005). The corresponding dose-response relationships were also significant, suggesting that vegetables and fruits rich in lycopene and other carotenoids may be protective against prostate cancer (Jian et al. 2005). In another study, it has been shown that a higher intake of lycopenes, the agent in tomatoes and beets that gives them their red color, has been shown to decrease risk of prostate cancer (Gann et al. 1999). In a large study of food intake and risk of prostate cancer, Giovannucci and colleagues (1995) demonstrated an inverse relationship between consumption of
lycopenes and the risk of prostate cancer. The major dietary sources of lycopenes are cooked tomatoes, tomato juice, and paste. The role of vitamin A in prostate cancer growth is less established (Reichman et al. 1990). In a multicentric, multi-ethnic population based case control study, it was found that intake of legumes, yellow-orange, and cruciferous vegetables was associated with a lower risk of prostate cancer (Kolenel et al. 2000). Another prospective study of Seventh-day Adventist men (Mills et al. 1989), it was found that consumption dietary items such as beans, lentils, peas, and tomatoes were significantly associated with lower risk for prostate cancer. A variety of carotenoids, including lycopene, inhibit prostate cancer cells in vitro (Yip et al. 1999).

In a case-control study in Japan (Ohno et al. 1988), fruit consumption was associated with a moderate increase in prostate cancer risk. In another case control study in Japan, consumption of fruits, all vegetables, green-yellow vegetables, and tomatoes showed no association, but the study supported the hypothesis that the traditional Japanese diet, which is rich in soybean products and fish, might be protective against prostate cancer (Sonoda et al. 2004). A case-control study from Canada (Jain et al. 1999) reported a statistically significant positive association between prostate cancer and the intake of total fruit, citrus fruit, and fruit other than citrus. Fruits and fruit juices as a single category were significantly positively associated with prostate cancer in another recent Canadian case-control study (Villeneuve et al. 1999). Fresh fruit showed no association with prostate cancer in a case-control study in Italy (Talamini et al. 1986), and the mean weekly consumption of total fruits was similar for cases and controls in a study conducted in China (Lee et al. 1999). Among cohort investigations, no clear association with total fruit intake was seen in five studies (Snowdon et al. 1984, Shibata et al. 1992, Hsing et al. 1990b, Mills et al. 1989, Giovannucci et al. 1995). In a subsequent report on one of these cohorts (Giovannucci et al. 1995), a protective effect against advanced prostate cancer was seen for fruits; this finding was accounted for by fructose intake (Giovannucci et al. 1998b). Two other cohorts (Severson et al. 1989, Schuurman et al. 1998) found an increased risk associated with total fruit intake; the result was statistically significant in one of these studies (Schuurman et al. 1998). One cohort study (Mills et al. 1989) found a weak inverse association for dried fruits (raisins, dates, and others); another (Severson et al. 1989) found a statistically significant increase in risk for citrus fruits. Thus, at the present time, evidence in support of a beneficial role of fruits for prostate cancer is very limited, and the data are inconsistent. While individual nutrients have been studied for their effects on risk, data from the European Prospective Investigation into Cancer and Nutrition (EPIC) showed no
association between total fruit and vegetable intake and prostate cancer risk among 130,000 men (Key et al. 2004).

The findings from prospective cohort studies are also inconclusive. Two studies found no association for total vegetables (Snodon et al. 1984, Shibata et al. 1992), and one study found no association for cruciferous vegetables in particular (Hsing et al. 1990). A study in Japan reported a protective effect of green-yellow vegetables in men, 75 years of age, whereas a study of Japanese men in Hawaii (Severson et al. 1989) reported an increased risk in men with higher seaweed consumption. Two cohort studies found an inverse association with the consumption of tomatoes but not of total vegetables or of other specific vegetables (Mills et al. 1989, Giovannucci et al. 1995). A recent study from the Netherlands (Schuurman et al. 1998) found no overall association with vegetable intake.

Explanations for the associations with specific vegetables must be speculative, because the present analysis was not designed to examine specific food constituents. Various factors may contribute to some of the inconsistencies in the association of fruits and vegetable intakes and prostate cancer, including nature of the studies, insufficient sample size, selection bias, measurement bias, recall bias, and heterogeneity of prostate cancer. The type of fruits and vegetables consumed by cases and controls may vary and it is difficult to ascertain whether the overall estimates are reliable for the observed protective effect. However, these results may give clues for further investigations.

7.2.3.2 Fish

Increasing evidence from animal and in vitro studies indicates that n-3 fatty acids, especially the long-chain polyunsaturated fatty acids, eicosapentaenoic acid and docosahexaenoic acid, present in fatty fish and fish oils inhibit carcinogenesis (Larsson et al. 2004, Rose and Connolly 1991, Connolly et al. 1997, Nobmann et al. 1992). Data from studies on humans have been sparse. Populations with a high consumption of fish, for example in Japan and among Eskimos in Alaska, have lower incidence rates of prostate cancer than populations with Western food habits, where fish intake in general is lower (Nobmann et al. 1992, Lanier et al. 1989, Nutting et al. 1993, Mishina et al. 1985). Many epidemiological studies showed a protective effect of intake of fish oil with prostate cancer (Norrish et al. 2000, Norrish et al. 1999). In a case control study conducted in Japan, consumption of fish showed significantly decreasing linear trends for risk (Sonoda et al. 2004).
Previous epidemiological studies on consumption of fish and prostate cancer have mostly been conducted in Western countries and have yielded inconsistent findings (Key et al. 1997, Anderson et al. 1995, Terry et al. 2001). Some studies showed a positive association. In a prospective study conducted in Japan, fish intake was significantly associated with an increased risk of prostate cancer; men who consumed fish more than four times per week had an increased risk of developing prostate cancer compared with men who ate fish less than twice per week (Allen et al. 2004). Human studies of body tissue levels of very-long-chain n-3 fatty acids and fish intake (Giovannucci et al. 1993a, Gann et al. 1994, Harvey et al. 1997) showed no association with prostate cancer risk. The incidence of prostate cancer in Europe and North America is high. In epidemiological studies from these regions, an intake of fish once per week or more often, as compared with an intake of less than once per week, has yielded inconsistent results (Key et al. 1997, Anderson et al. 1995, Terry et al. 2001, Hsing et al. 1990, Fernandes et al. 1999).

The present study showed that consumption of fish either more or less quantities were not significantly associated with prostate cancer, a finding consistent with few of the previous studies. In view of limitations and biases mentioned earlier, the evidence provided in this study may not be a strong one, however.

7.2.3.3 Meat

Intake of meat is positively associated with prostate cancer in some studies. In a case control study conducted in Japan, consumption of meat was significantly associated with increased risk (Sonoda et al. 2004). In the Health Professionals Follow-up study (Giovannucci et al. 1993a), a significant positive association was found for red meat intake. This led researchers to believe that the preparation of this food or other components in meat were responsible for the excess risk. For example, a variety of carcinogens produced during the cooking of animal fat may be responsible for the increased risk (Sugimura 1985, Shirai et al. 1997). In addition, this and other meats are also a significant source of certain minerals (zinc and calcium), which may be associated with a further increased risk (Shils et al. 1994, Giovannucci et al. 1998b). In a prospective investigation (Gann et al. 1994) – the Physicians' Health Study – also found an association between red meat intake and risk of prostate cancer, but this was not statistically significant. In a cohort study of Norwegian men (Veierod et al. 1997), a significant risk was observed in those men who consumed main meals of hamburger/meatballs. However, an inverse relationship was found among
men who included meat in their main meals. This could have been a chance discovery, or may partly support the cooking method and risk hypothesis. The best evidence for a dietary basis to the development of prostate cancer comes from a prospective study based in the Netherlands. With cured meat and milk products found to be significant risk factors for the development of this disease (Schuurman et al. 1999b), but some other studies show no association (Norrish et al. 1999). Studies in which high intake of red meat raises the risk for prostate cancer may be because red meat is often in fat, and this fat may be increasing the risk. Such findings may explain the inconsistencies found in studies that simply look at meat as a risk for prostate cancer. Perhaps of more importance, high-temperature cooking (grilling, broiling, or pan-frying) of meat or poultry has been specifically associated with increased risk for cancer in some studies. Over-cooking meat increases the amount of compounds called heterocyclic amines, which has been associated with cancerous changes in general and prostate cancer in particular, at least in some studies. Cooking meats in liquid does not appear to increase these compounds. As with all dietary studies, some have observed no association between high intake of well-cooked meat and prostate cancer.

In the present study there was no statistically significant association of meat intake with prostate cancer. Thus, this is a controversial area that requires more research. It is difficult to draw firm conclusions from these epidemiology studies, because of the greater potential for recall bias, measurement bias and confounding. Therefore, large-scale prospective studies are still required to shed some light on this issue.

7.2.3.4 Tea and coffee

Some epidemiological observations have suggested that people who consume tea regularly have a lower risk of prostate cancer (Heilbrun et al. 1986, Severson et al. 1989). Second, the incidence of prostate cancer in China, a population that consumes green tea on a regular basis, is lowest in the world (Gupta et al. 1999). In one recent study, tea consumption showed an increase in prostate cancer risk (Sharpe and Siemiatychi 2002). Many other studies showed no association between tea consumption and prostate cancer development (Kinlen et al. 1988, Severson et al. 1989, La Vecchia et al. 1992, Talamini et al. 1992, Slattery and West 1993, Jain et al. 1998, Villeneuve et al. 1999, Ellison 2000), a finding consistent with the findings of the present study. Also the results of the present study were consistent with those of the other studies on coffee consumption (Nomura et al. 1986, Severson et al. 1989, Fincham et al. 1990, Hsing et al. 1990b, Talamini et al. 1992, Slattery
Biological evidence suggests that non-alcoholic beverages, both coffee and tea are mutagenic (Nagao et al. 1979), subcutaneously injected tannic acid is carcinogenic in rodents (IARC 1975), and some carbonated beverages contain methylglyoxal, a genotoxin (IARC 1991). However, in vitro experiments suggest that components of tea could interfere with the development of prostate cancer (Ren et al. 2000). Thus, some data indicate that coffee and tea consumption could initiate cancer on the one hand, and that tea consumption could prevent prostate cancer on the other. Because of limited assessment of these exposures in epidemiologic studies, the human evidence remains inconclusive (Blot et al. 1996).

7.2.3.5 Oil/Fat

Results from several case-control and cohort studies on fat intake and risk of prostate cancer have been inconsistent. Evidence from many case-control studies has generally found an association between dietary fat and prostate cancer risk (Rose et al. 1986, Kolonel et al. 1988), although some studies have not uniformly reached this conclusion (Schuurman et al. 1999a, Giovannucci et al. 1995, Mettlin et al. 1989, Severson et al. 1989). In a recent review of the topic, 11 of 17 case-control studies showed a positive association between prostate cancer and fat intake; none showed a negative association (Yip et al. 1999). In a review of published studies of the relationship between dietary fat and prostate cancer risk, among descriptive studies, approximately half found an increased risk with increased dietary fat and half found no association (Zhou and Blackburn 1997). In general, fat of animal origin seems to be associated with the highest risk (Optenberg et al. 1995, Rose et al. 1986). In a series of patients with prostate cancer, the risk of cancer progression to an advanced stage was greater in men with a high fat intake (Bairati et al. 1998). In another study of men in Hawaii, a significant association was seen between prostate cancer mortality and dietary fat in men over 70 years old (Cole and Rodu 1996, Wynder and Cohen 1997). The announcement in 1996 that cancer mortality rates had fallen in the United States prompted one suggestion that this may be due to decreases in dietary fat over the same time period (Cole and Rodu 1996, Wynder and Cohen 1997). In the Health Professionals Follow-up Study, a positive association was seen between intake of red meat, total fat, and animal fat, and the incidence of prostate cancer (Giovannucci et al. 1993a). A recent investigation was from Saudi Arabia (Hanash et al. 2000) and this study showed no relationship between fat intake, mainly from meat and dairy products and prostate cancer
risk. The authors of that study did comment that fiber, cereals, cooked tomatoes, rice, tea, fruits and vegetables, among other dietary items that are low in fat, are consumed in large quantities in the average Saudi diet. These healthy items could have been responsible for the lack of an association between fat and prostate cancer.

Studies in some animal models (Wang et al. 1995, Pollard and Luckert 1986), conducted to examine the relationship between prostate cancer and diet, have found an inhibition of tumor growth with a lower fat intake, or an increased growth with a high fat intake. However, other animal studies that have ensured isonutrient intakes (Pour et al. 1991, Clinton et al. 1997) have not been able to effect the growth of transplanted prostate tumors, or the induction of such cancer by increasing dietary fat. In another extensive animal study (Mukherjee et al. 1999) found that cancer growth was independent of the percentage of fat in the diet, as long as the total energy intake was restricted. The reduction observed in cancer growth was actually similar in all types of energy-restricted laboratory animals. These experiments suggest an overall reduction in energy intake, and not just in fat per se, is the best method to reduce the risk or progression of prostate cancer (Bosland et al. 1999). These studies also suggest that fat in combination with some other unknown dietary factor(s) may be responsible for increasing tumor growth. Even though not statistically significant, the present study indicated that more quantities of oil/fat consumption (more than 2 kg oil/fat per month) is associated with an elevated risk for prostate cancer, a finding consistent with many of the previous studies on fat consumption and prostate cancer risk.

The explanation for this possible association between prostate cancer and dietary fat is unknown. Several hypotheses have been advanced including:

1. **Dietary fat may increase serum androgen levels, thereby increasing prostate cancer risk.** This hypothesis is supported by observations from South Africa and the United States that changes in dietary fat change urinary and serum levels of androgens (Hill et al. 1979, Hamalainen et al. 1984).

2. **Certain types of fatty acids or their metabolites may initiate or promote prostate carcinoma development**. The evidence for this hypothesis is conflicting, but one study suggests that linoleic acid (omega-6 polyunsaturated fatty acid) may stimulate prostate cancer cells while omega-3 fatty acids inhibit cell growth (Rose and Connolly 1991).

3. **An observation made in an animal model is that male offspring of pregnant rats fed a high-fat diet will develop prostate cancer at a higher rate than animals fed a low-fat diet** (Kondo et al. 1994). This observation may explain some of the variations in prostate cancer incidence and mortality among ethnic groups. An observation has been made that first trimester androgen levels in pregnant blacks are higher than those in whites (Henderson et al. 1998).
Much epidemiologic and case-controlled evidence suggests that diet may be a modifier of prostate cancer risk. Nutrition is apparently a major risk factor for the development and progression of prostate cancer. Based on experimental studies and epidemiologic data mainly from case-control studies or cohort studies, there is strong evidence that reduction of the total energy consumption, a diet comprising less than 30% fat, and increased intake of phytoestrogens, vitamins D and E and selenium could yield a decreased prostate cancer incidence. The traditional Mediterranean diet has many of the right elements (Meister et al. 2002).

The term ‘the Mediterranean diet’ was first popularized by Ancel Keys in his book *How to Eat Well and Stay Well: the Mediterranean Way*, in 1975. This followed the publication of his studies which showed that Mediterranean countries have diets associated with low incidence of cancer and cardiovascular disease.

There is now little doubt that the Mediterranean countries enjoy a low risk of many of the diet-related diseases of affluence (Hill and Giacosa 1992, Hu 2003).

The Mediterranean is a large area with many different diet patterns, but they are all characterized by high consumption of fruit, vegetables, legumes and dietary fibre and low intakes of meat and saturated fats. In all of these respects they agree with the current concepts of a ‘healthy diet’ and one towards which many countries in northern Europe are moving (Trichopoulou 2001).

### 7.2.4 Tobacco habits

In a recent cohort study (Putnam et al. 2000) and another multicentre case control study (Hayes et al. 1996), it has been found that tobacco use is not associated with risk of prostate cancer. Another case control study by Gronberg et al. (1996), showed that neither tobacco nor alcohol use substantially changes the risk of prostate cancer. In a population based case control study by Sharpe and Siemiatycki (2001), it has been found that tobacco smoking is positively associated with prostate cancer risk. Dozens of other studies have failed to demonstrate a consistent relationship between cigarette smoking and prostate cancer (Hickey et al. 2001). Most studies have found no important difference in prostate cancer rates between smokers and nonsmokers or have shown only a small excess of prostate cancers among smokers. Hsing and co-workers (1990a) observed an increased relative risk of prostate cancer for cigarette smoking and for chewing tobacco. Coughlin and colleagues (1996) observed in their study that the risk of developing prostate cancer was slightly
increased among men with a history of smoking. Some epidemiological cohort studies that
have shown a relationship between cigarette smoking and death from prostate cancer
(Giovannucci et al. 1999, Rodriques et al. 1997, Hsing et al. 1991, Daniell 1995). In a 26-
year followup of veterans, Hsing et al demonstrated a dose dependent association of
cigarette use and prostate cancer mortality (Hsing et al. 1991). Giovannucci et al. (1999)
found that men with a greater smoking history in the prior 10 years had a greater risk of
metastatic prostate cancer and fatal prostate cancer.

Because tobacco smoking is an established risk factor for a wide variety of cancers,
researchers have considered the possibility that it may be linked with prostate cancer as
well. However, the evidence for such an association is weak at best (Meister et al. 2002).
Compared to its very strong impact on carcinogenesis of other organs, it appears that
cigarette smoking adds little, if any, to the risk of developing prostate cancer (Lumey
1996). Any small excess could easily be attributable to increased diagnosis of latent
prostate cancers among smokers. Because smokers tend to have more health problems than
nonsmokers do, they go to the doctor more often and therefore may be more likely to be
tested for prostate cancer. The present study showed no statistically significant association
for tobacco smoking, neither bidi smoking or cigarette smoking or tobacco chewing with
prostate cancer. There were no dose response relationship with number of bidi or cigarette
smoked and also time since start of bidi or cigarette smoking habits. These findings were
consistent with few of the earlier studies. Due to the several limitations and biases in the
present study, the evidence for the observed association may not be a strong one.

7.2.5 Alcohol habits

In the 1960s, it was suggested that heavy consumption of alcohol might reduce the risk of
prostate cancer, perhaps by lowering male hormone (androgen) levels in the body. A
biologically plausible protective role for alcohol in prostate carcinogenesis has been
hypothesised from reports that alcohol may increase metabolic clearance of testosterone
(Gordon et al. 1976). More recently (Putnam et al. 2000), it has been suggested that heavy
intake of alcohol might increase prostate cancer risk by interfering with nutrition or by
reducing the ability of the liver to detoxify cancer-causing agents. A large population-based
case-control study reported evidence of a dose-response relation between alcoholic
beverage consumption and risk of prostate cancer (Hayes et al. 1996). In a recent
epidemiologic study, a positive association was found between moderate alcohol
consumption and the risk of prostate cancer. Liquor, but not wine or beer, consumption was positively associated with prostate cancer (Sesso et al. 2001). A case control study by Gronberg et al. (1996), showed that alcohol use did not have any effect on the risk of prostate cancer which is consistent with the present study findings. The present study showed no statistically consistent association for alcohol drinking habits with prostate cancer and no dose-response relationship for number of times and time since start of wine, whisky and toddy drinking habits. While the epidemiological literature generally does not support a relation (Breslow and Weed 1998), the common occurrence of this cancer coupled with the routine use of alcohol in many populations means that even a moderate effect may be of public health significance. Further Investigations of the relationship of alcohol intake to prostate cancer are needed.
The International Agency for Research on Cancer has provided data on Global cancer burden and time trends of various cancers in different parts of the world. The cancer registries under the NCRP network of the Indian Council of Medical Research have provided data on the magnitude of the cancer problem in India. They are also serving as the base in taking measures for prevention and control of cancer in India.

The data from cancer registries have indicated that cancer of the prostate is one of the most common malignancies among elderly men with a rising time trend in many areas. Although many studies on prostate cancer have been conducted in different parts of the world, the aetiology of this disease is largely unknown. Age >50 years, being an African-American and a family history of prostate cancer are considered to be as established risk factors for prostate cancer. Other factors such as vasectomy, marital history, dietary habits, tobacco use, alcohol intake, etc. have conflicting evidence on the association of prostate cancer.

This study was conducted at Bombay Population Based Cancer Registry (PBCR), located at Mumbai, which is the capital of the state of Maharashtra. The Bombay PBCR is the first Population Based Cancer Registry established in India in June 1963, as a unit of the Indian Cancer Society, at Mumbai, with the aim of obtaining reliable morbidity and mortality data on cancer from a precisely defined urban population (Greater Mumbai). It is also one of the oldest and biggest Population Based Cancer Registries in the world.

In this study we included only microscopically proved incident cases of prostate cancer registered in the specified time span and in the geographical area covered by the Bombay Population Based Cancer Registry. The area covered by this registry is one of the districts of Maharashtra state having 100% urban population. The data collected by the Bombay Cancer Registry has been shown both complete and reliable. So the study base is of acceptable standard.

The present study was conducted to assess the role of vasectomy, marital history, dietary habits, tobacco use, and alcohol consumption on prostate cancer in a relatively low risk population of a developing country. The results were:
Vasectomy has been emerged as a risk factor for prostate cancer. Compared with no vasectomy the OR for ever having undergone vasectomy was 1.9 after controlling for age and other possible confounding factors. The risk for those who had a vasectomy before the age of 45 years was 2.1 fold and those who had it at a later age (45 years or later) was 1.8 fold compared to those who did not had a vasectomy. Also those who had completed more than 2 decades after had a vasectomy showed a 3.8 fold risk for prostate cancer compared to those who did not had a vasectomy.

Late marriage, that is, men who married at the age of 25 years or later, were associated with a 2.5 fold risk for prostate cancer compared with those who married at younger ages, before the age of 25 years.

The role of certain dietary factors including fruits and vegetables, fish, meat, coffee, tea and oil/fat intake on prostate cancer indicated that those who consumed more than 2 kilograms of fruits and vegetables in a week showed a protective effect for prostate cancer compared to those who consumed less than 2 kilograms of fruits and vegetables and the dose response was statistically significant, intake of fish, meat showed no statistically significant association with prostate cancer, consumption of non-alcoholic beverages like coffee, tea were not significantly associated with prostate cancer but high quantities of oil/fat consumption (more than 2 kilograms of oil/fat per month) showed an insignificant increased risk for prostate cancer.

Tobacco smoking or tobacco chewing showed no statistically significant association with prostate cancer. Also there were no dose response relationships for number of bidi, cigarette smoked or time since start of these habits.

Alcohol drinking (wine, whisky or toddy) did not show any statistically significant association with prostate cancer neither any dose response was observed for number of times drank or time since start of these habits.

The life style and dietary habits included in this study have several limitations as discussed earlier. The changing life style and dietary habits of people are very complex and vary from person to person. It is difficult to ascertain whether the estimates obtained for one factor is an absolute estimate or confounded by many other factors directly or indirectly. A look on the correlation of the factors under study revealed that all factors are correlated at varying levels and when there is a high correlation between two factors, it is difficult to assess whether the estimates obtained are due to the one or the other and we can only assess that it may be due to either of the two. There were deficiencies in filling of the questionnaire especially for some components of tobacco and alcohol habits. The unusual correlation among different alcohol habits (such as a negative correlation among whisky
drinkers and wine drinkers) were also suggestive of deficiencies in abstracting this information. In the questionnaire, for some components of alcohol and tobacco, only known habits were being filled and all the remaining being kept blank. It was impossible to separate out ‘no habits’ and ‘unknown habits’ from these blanks and in the analysis, all these blanks were interpreted as ‘no habits’. However, this was not selective for cases and controls. Due to the several limitations and possibilities for biases in this study, the evidence for the estimates obtained may not be a strong one, however, these results may give clues for further investigations and so prospective studies with good design and conduct are required for a better understanding of the etiology of prostate carcinogenesis.

As discussed earlier, it is important to note certain limitations especially for vasectomy. Potential information bias from proxy respondents is a concern in this study. The results from additional analysis restricted to direct respondents yielded an adjusted but insignificant (the statistical insignificance can be due to the decrease in sample size) odds ratio of 1.4, indicating a substantial reduction in risk compared with the results (OR 1.9, 95% CI 1.3-2.9) from including proxy respondents.

Reporting bias may account for the difference in estimates of risk based on information reported by self and by a proxy. It is important to note that for 40% of the cases who were dead or in advanced conditions, the information was reported by proxies and since vasectomy is a sort of operation and the cases were seriously hospitalised, the proxies might have tended to answer positive for vasectomy. This might have caused over reporting of vasectomy for cases. The controls were all younger and healthy persons and because vasectomy was self reported, there is possibility for under reporting since vasectomy is a very personal and in fact humiliating a man’s personality to express in front of family members and relatives. The dose response relationship on age at vasectomy and time since vasectomy may also be due to some psychosocial background, the crudest family planning policy occurred in the youth of these men. It may also have been especially embarrassing to have vasectomy at a young age.

The impact of any reduction in popularity of vasectomy attributable to concerns regarding prostate cancer is most likely to be felt in developing countries, particularly in several countries in Asia and Africa where maternal and infant mortality rates are high and vasectomy programs are just beginning to grow. If vasectomy is a risk factor for prostate cancer, people need to know and informed choices need to be made. By contrast, if associations are spurious but believed to be real, the popularity of a highly effective contraceptive will be reduced, opportunities to reduce unintended pregnancy will be lost, and maternal and infant mortality and morbidity will increase. Due to the several
limitations and possibilities for reporting biases in this study, the evidence for the estimates of the higher odds ratio for prostate cancer in vasectomised men may not be a strong one. Because of the importance of vasectomy for fertility control, further studies with good design and conduct (the information on vasectomy need to be collected with better reliability) are required to clarify the issue of vasectomy associations with prostate cancer.
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAR</td>
<td>Age adjusted rate</td>
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<tr>
<td>ATBC</td>
<td>Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>CR</td>
<td>Crude rate</td>
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<td>DRE</td>
<td>Digital rectal examination</td>
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<td>FDA</td>
<td>Food and drug administration</td>
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<td>HBCR</td>
<td>Hospital Based Cancer Registry</td>
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<td>IARC</td>
<td>International Agency for Research on Cancer</td>
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<td>IIPS</td>
<td>International Institute for Population Sciences</td>
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<td>ICMR</td>
<td>Indian Council of Medical Research</td>
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<td>LPA</td>
<td>Leisure time physical activity</td>
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<td>NCRP</td>
<td>National Cancer Registry Project</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PBCR</td>
<td>Population Based Cancer Registry</td>
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<td>PIN</td>
<td>Prostate intraepithelial neoplasia</td>
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<td>PLCO</td>
<td>Prostate, Lung, Colorectal and Ovarian (Cancer Screening Trial)</td>
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<td>PRC</td>
<td>Population Research Centre</td>
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<td>PSA</td>
<td>Prostate specific antigen</td>
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<td>TRUS</td>
<td>Trans rectal ultrasound</td>
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<td>UK</td>
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<td>USA</td>
<td>United States of America</td>
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Tampere, September, 2005

Lizzy Sunny
REFERENCES


